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The American Journal of CARDIOLOGY®

25th Anniversary

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A YORKE MEDICAL JOURNAL

A THERAPEUTIC STEP AHEAD

LOPID®
(gemfibrozil)

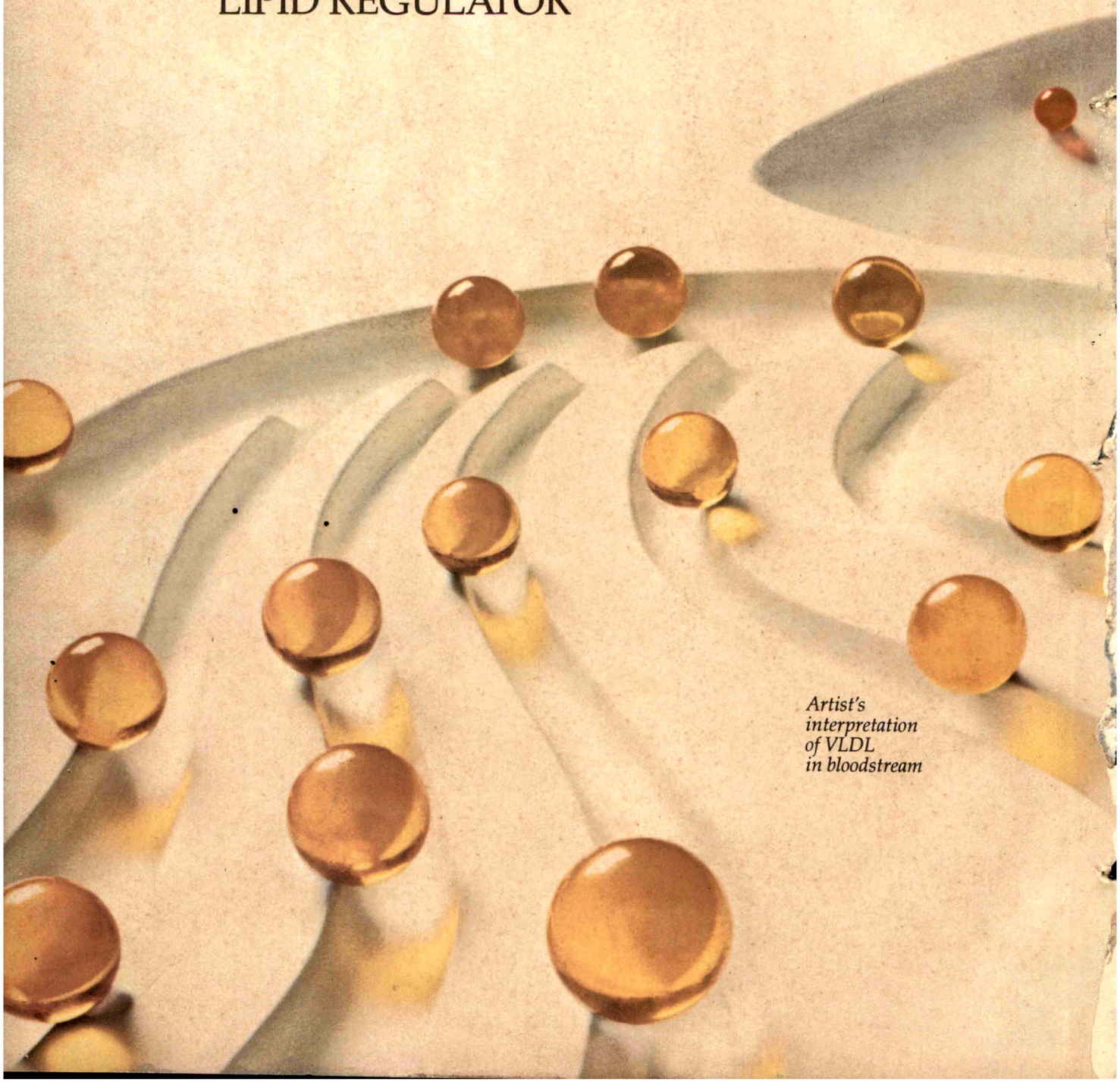
MORE THAN A LIPID-LOWERING AGENT— A TWO-WAY LIPID REGULATOR

Favorably regulates the balance of lipid fractions in certain dyslipidemias:

1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent, cholesterol-rich LDL (very-low- and low-density lipoproteins implicated in dyslipidemia)

2/May also RAISE serum levels of HDL (high-density lipoproteins believed to transport cholesterol to the liver for catabolism and excretion)

LOPID is indicated for treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.

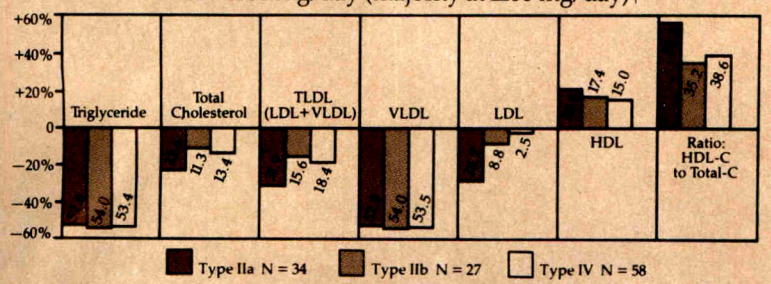


Artist's interpretation of VLDL in bloodstream

Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†



*Visit every 4 weeks during long-term use of LOPID.

†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

Convenient BID dosage

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

Reference:

1. Data on file, Medical Affairs Dept, Parke-Davis.

Artist's interpretation of HDL in bloodstream

LOPID® 300-mg capsules

(gemfibrozil)

PARKE-DAVIS

Please see following pages for brief summary of prescribing information.

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P24,134

LOPID® (gemfibrozil)
A LIPID REGULATOR

LOPID® (gemfibrozil) Capsules

Before prescribing, please see full prescribing information.
A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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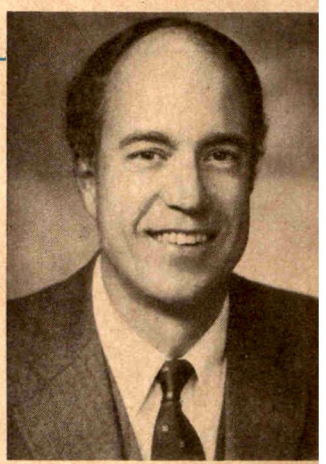

The Summary: The Manuscript's Bottom Line

Through the years I have asked numerous readers of medical journals which journal they read monthly and how they select which articles to read in a particular journal. The responses to the latter question indicate that the most frequent portion of a manuscript read is the manuscript's title, and next the manuscript's summary. If the latter is unappealing, most readers do not pursue other portions of the manuscript. But is the summary given the same attention by the author as it is given by the reader? I think not.

When writing medical papers with young associates, rarely have I been presented with a rough draft of a manuscript containing a summary. The summary, I suspect, tends to be written by many authors just before the final typing of the manuscript. Thus, when written last, the summary tends to be disjointed as it attempts to tie together the important points of the paper. When written first, the summary serves as an outline, focusing the thrust of the manuscript. Moreover, by being done last, the summary may not receive the thoughtful deliberation given other portions of the manuscript.

Because the summary is so important to a manuscript, I suggest that an author write this portion *first* (after the title) rather than last. By so doing, one may focus better on the number of points the particular manuscript is trying to make. If the manuscript has essentially only 1 point, the summary can be particularly crisp and short; if more than 1 point, the summary provides an outline of the points to be made. After the point or points of the manuscript are clearly in focus, the remainder of the paper can more readily build the case demonstrating the validity of each point. The summary then needs to be given the same emphasis and importance by authors as it receives from readers.

William C. Roberts

William C. Roberts, MD
Editor-in-Chief

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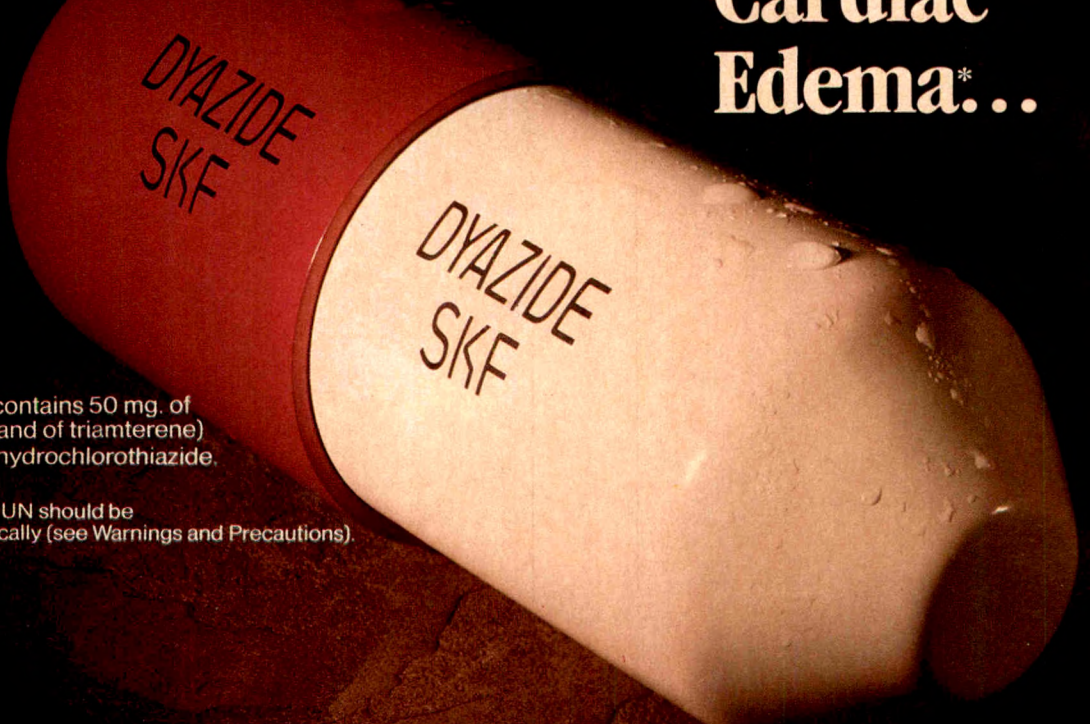
In Cardiac Edema*...



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

When You Need to Conserve K+

Over 17 Years of Confidence

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both; hyperglycemia and glycosuria (diabetic insulin requirements may be altered); hyperuricemia and gout; digitalis intoxication (in hypokalemia); decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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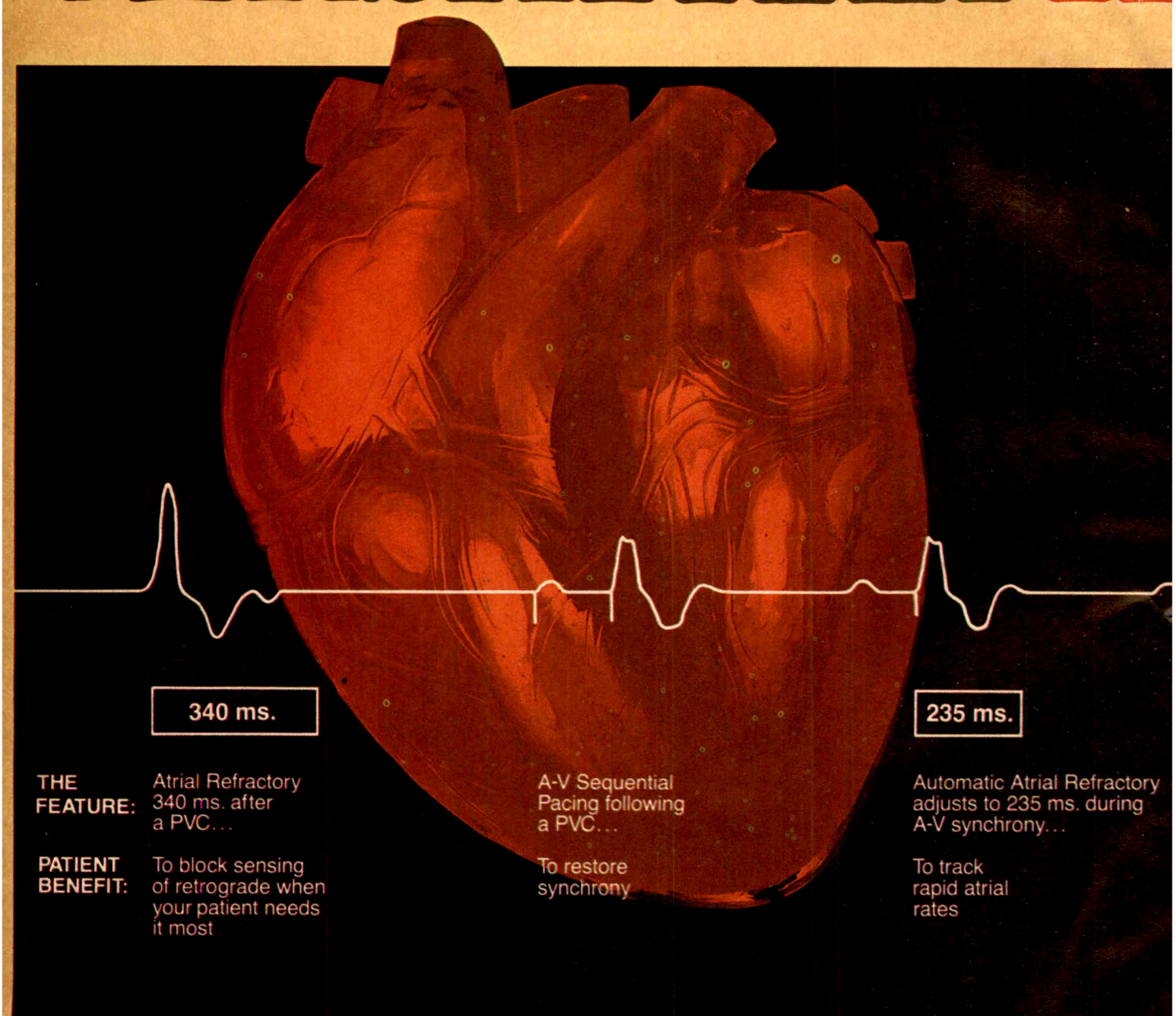
New VERSATRAX II



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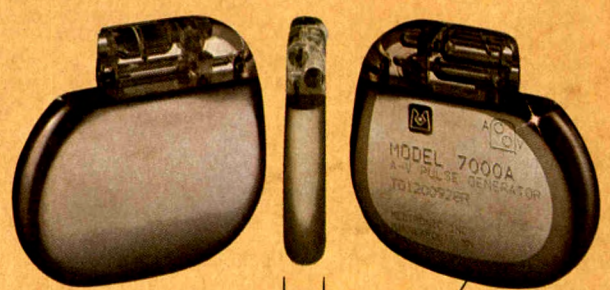

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The Model 7000A universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing where restoration of A-V synchrony and/or sinus modulated rate variability is indicated to improve cardiac output or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 7000A universal A-V pulse generator is under clinical investigation in the U.S. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Uses" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 7000A pulse generator during its clinical investigation. Patients should be advised that the Model 7000A pulse generator is under clinical investigation.

Contraindications

General: There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode: The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

DVI Mode: In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy: Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site.

Electrosurgical Units: Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

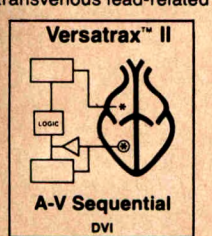
Defibrillation: Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. Positioning a magnet or the programming head over the pulse generator makes it subject to programming. A nominal vertical magnetic field strength of 90 Gauss (in a field measured 1½ inches from the magnet's surface) from a magnet at 1¼ inches from the reed switch is required to initiate asynchronous pacing. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pulse generator. If an electrocautery unit is used, the physician may prefer to program the pacemaker to asynchronous pacing prior to the procedure.

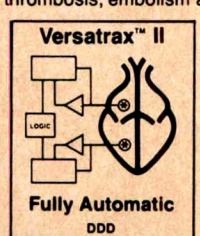
Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.





KEY TO SYMBOLS

◁ = Sensing Circuit
□ = Output Circuit
○ = Sensing
* = Stimulation

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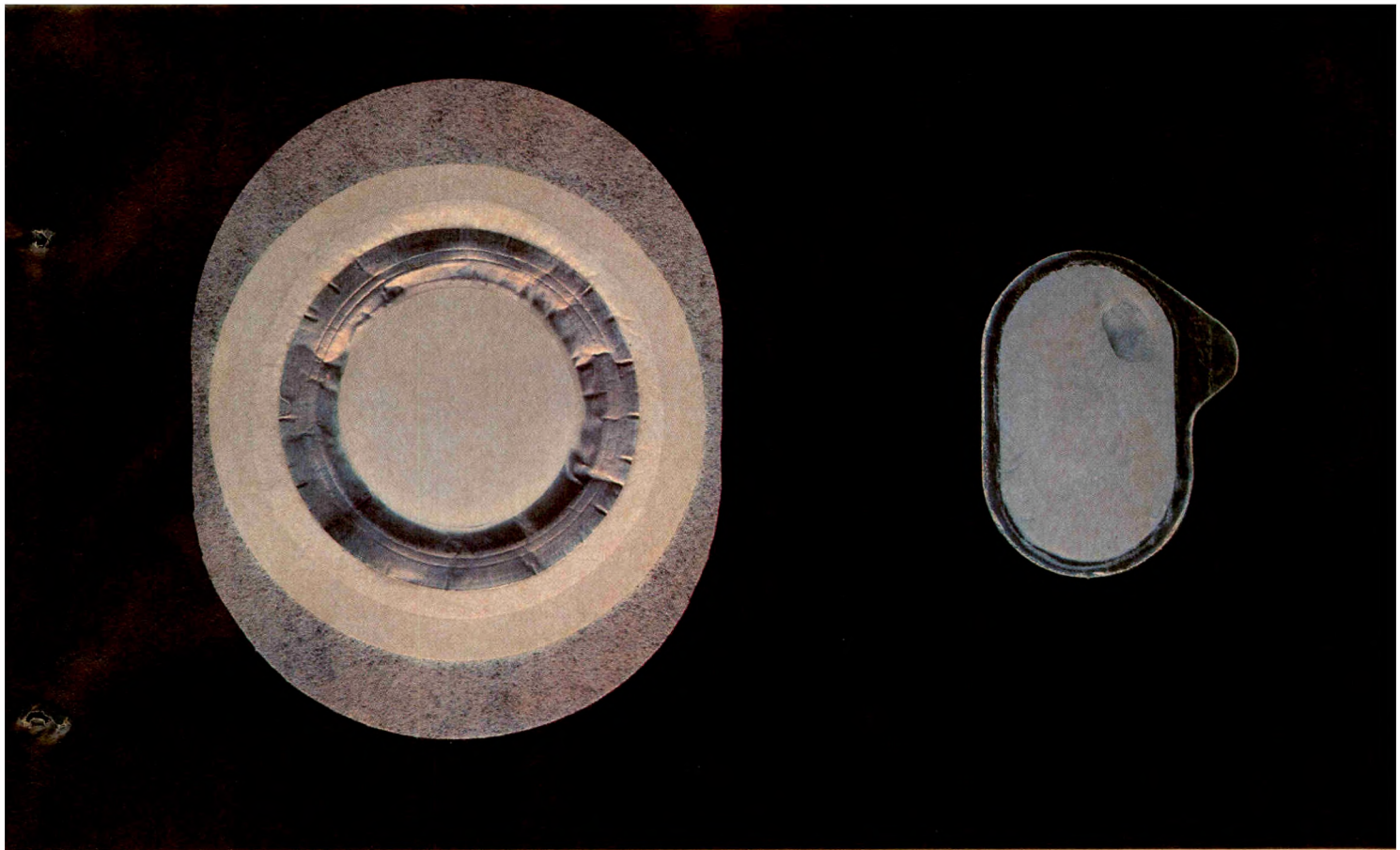
CORRECTION

In the May 1, 1983 issue on page 1377 (*Savage DD et al: Prevalence of Submitral [Anular] Calcium and its Correlates in a General Population-Based Sample [The Framingham Study]*), Table III contained 2 errors:

1. The data on atrial fibrillation are from offspring *and* original cohort subjects, whereas the remainder of the data in the Table are derived only from original cohort subjects.

2. Of the cohort subjects without submitral calcium, 6% (not 26%) had ≥ grade 3 murmurs.



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CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[1] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

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For complete prescribing information, please see package insert.

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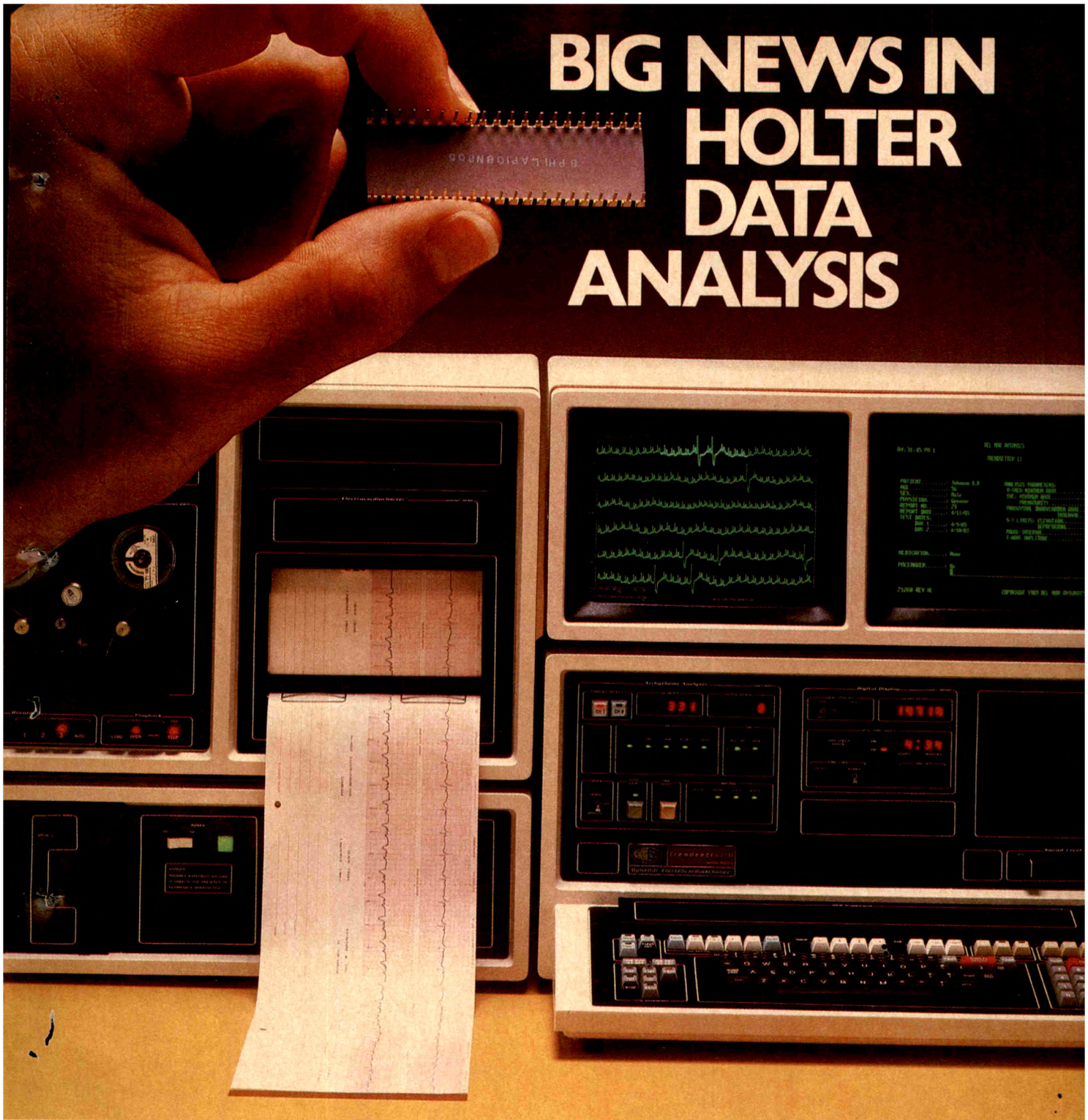

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The Trendsetter II System also features Express Trac,™ an advanced method of instantly analyzing and quantifying significant arrhythmia — with no operator intervention.

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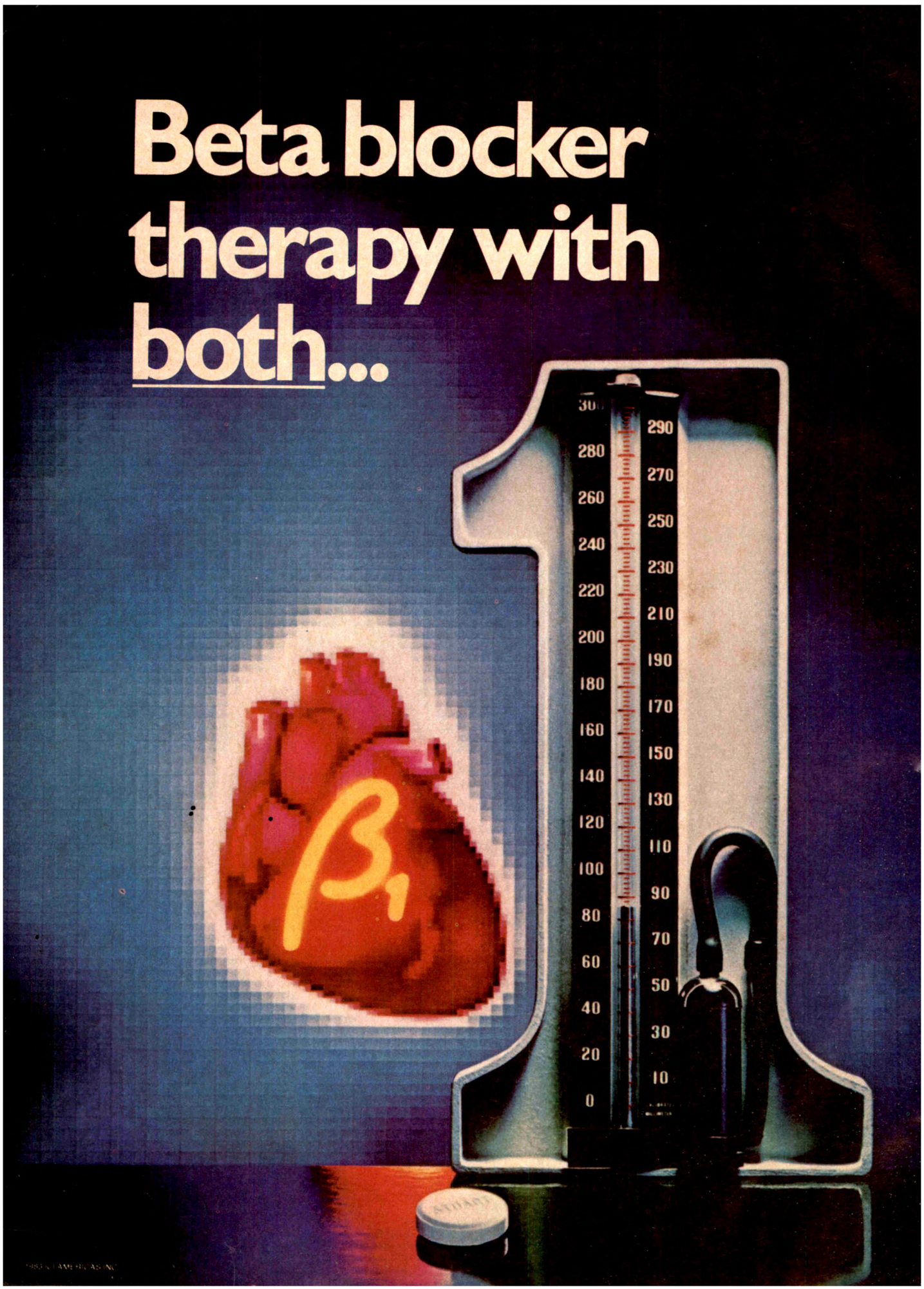

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cardioselectivity*

ONE TABLET A DAY

TENORMIN®

(atenolol)

Tablets 50 mg

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

See last page of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTIC

TENORMIN® (atenolol)

A beta$_1$-selective blocking agent for hypertension.

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m^2)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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VOLUME

CONTENTS

CORONARY HEART DISEASE

1 **Intracoronary Thrombus in Nontransmural Myocardial Infarction and in Unstable Angina Pectoris**

JAY B. MANDELKORN, NELSON M. WOLF, SURENDER SINGH, JAY A. SHECHTER, ROBERT I. KERSH, DAVID M. RODGERS, MARK B. WORKMAN, LAMBERTO G. BENTIVOGLIO, STEVEN M. LaPORTE, and STEVEN G. MEISTER, *With the technical assistance of* BARBARA TUCKER

To determine whether intracoronary thrombus occurs in nontransmural myocardial infarction (MI) or unstable angina pectoris (UA), coronary arteriography was performed before and after intracoronary nitroglycerin and streptokinase infusion in 17 patients. None of the 8 nontransmural MI patients and 1 of 9 patients with UA responded to intracoronary nitroglycerin. Seven nontransmural MI patients and 4 patients with UA responded to streptokinase infusion with opening of an occluded vessel, an increase in stenotic diameter, or dissolution of an intracoronary filling defect. Serial opening and closing of ischemia-related vessels occurred spontaneously and in response to streptokinase in some patients in whom thrombolysis was demonstrated. Evidence of thrombolysis was not seen in any patient studied longer than 1 week from the onset of the rest pain syndrome. The findings of thrombolysis in several patients with nontransmural MI and UA suggest that intracoronary thrombus formation plays a pathogenetic role in some patients with these ischemic syndromes.

7 **Comparison of High-Dose and Medium-Dose Propranolol in the Relief of Exercise-Induced Myocardial Ischemia**

KENNETH G. MORRIS, MICHAEL B. HIGGINBOTHAM, R. EDWARD COLEMAN, DAVID G. SHAND, and FREDERICK R. COBB

This study compared the effects of medium-dose (160 mg/day) and high-dose (480 mg/day) propranolol on symptoms and objective indexes of left ventricular ischemia in 22 males with coronary artery disease and typical angina pectoris. Patients were assessed at rest and during exercise to the pretreatment maximum work load. Medium-dose propranolol improved the functional class in 11 of 22 patients, reduced heart rate and blood pressure, and reduced the incidence of exercise-induced chest pain and electrocardiographic S-T segment depression. The radionuclide ejection fraction and wall motion score were unchanged at rest but were significantly improved during exercise. High-dose propranolol improved the functional class in 4 other patients and further reduced exercise-induced chest pain and S-T segment depression; the ejection fraction and wall motion score further improved in several other patients, although the change was not significant for the group. This study provides objective evidence that high doses of propranolol provide additional relief of ischemia and may improve symptoms in patients who do not respond to commonly used doses.

14 **Anatomic and Prognostic Significance of New T-Wave Inversion in Unstable Angina**

DAVID E. HAINES, DANIEL S. RAABE, WALTER D. GUNDEL, and FRANS J. Th. WACKERS

Patients with unstable angina may demonstrate gradual development of T-wave inversion without biochemical evidence of myocardial necrosis. In 118 consecutive patients with unstable angina, new T-wave inversion ($\geq$2 mm) occurred in 47 patients (40%). This finding was correlated with coronary angiographic findings and follow-up. In patients who underwent coronary angiography, new T-wave inversion in anterior leads correlated with significant stenosis of the left anterior descending coronary artery (sensitivity 69%, specificity 89%, and positive predictive value 86%). In patients who had follow-up on medical treatment, new T-wave inversion correlated with a significantly higher incidence of myocardial infarction and cardiac death. New T-wave inversion on the electrocardiogram of patients with unstable angina identifies a subgroup with significant coronary artery disease and a poor prognosis on medical treatment.

Continued on page A21

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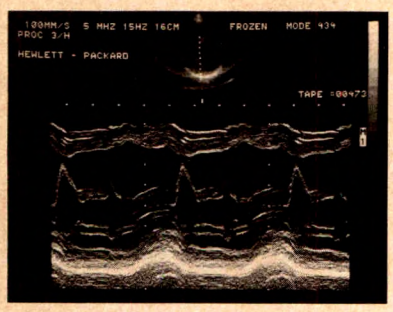

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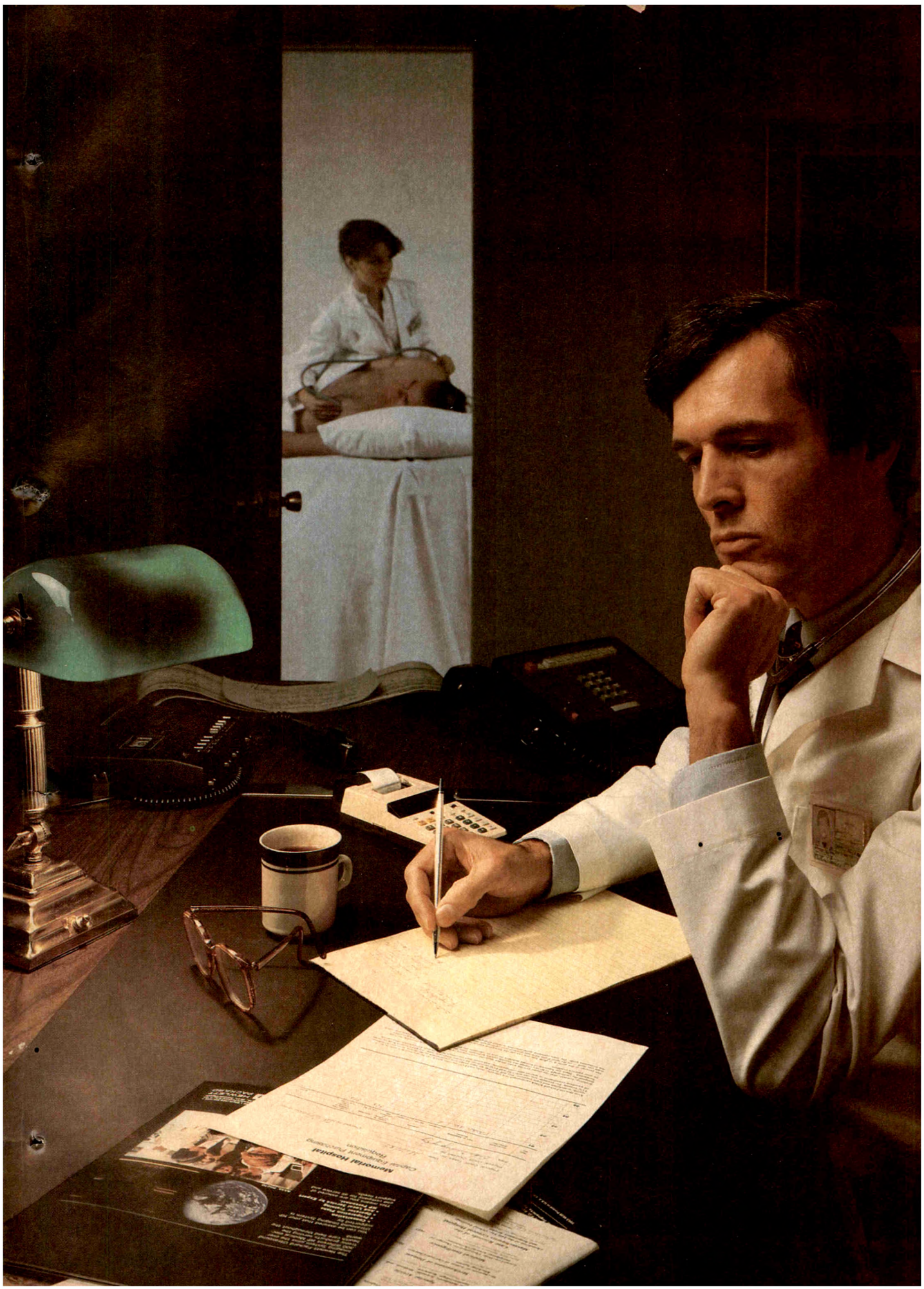
Memorial Hospital
Cancer Treatment Procedure
Radiation

Indications: Premature atrial and ventricular contractions, aproxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, paroxysmal ventricular tachycardia when not associated with complete heartblock, maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting in extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, light-headedness, and tremor; (3) G.I. symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at the rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G.I. symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 (NDC 0031-6649-63) and 250 (NDC 0031-6649-67) and Dis-co® Unit Dose Packs of 100 (NDC 0031-6649-64).

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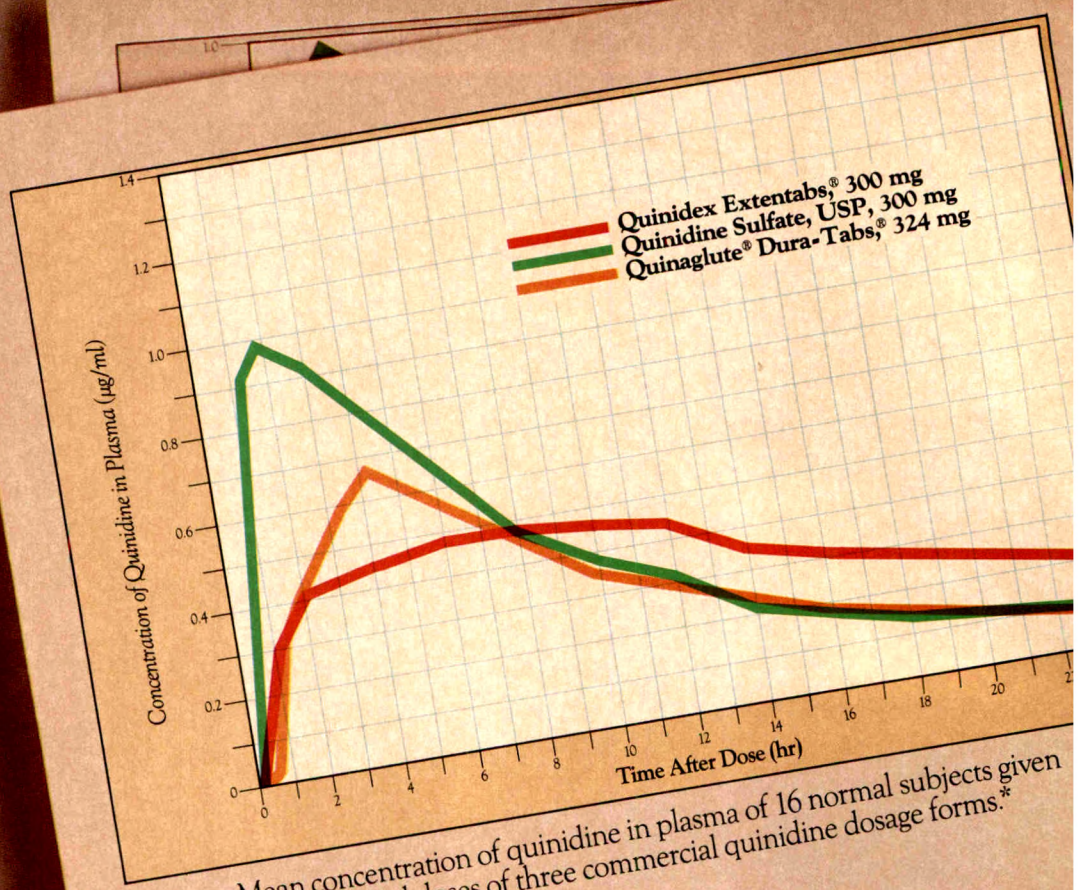

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19 **Ventricular Tachyarrhythmias in Prinzmetal's Variant Angina: Clinical Significance and Relation to the Degree and Time Course of S-T Segment Elevation**

MARIO PREVITALI, CATHERINE KLERSY, JORGE A. SALERNO, MARCELLO CHIMIENTI, CLAUDIO PANCIROLI, EGIDIO MARANGONI, GIUSEPPE SPECCHIA, MARIO COMOLLI, and PIERO BOBBA

Ventricular tachyarrhythmias were documented during ischemic attacks in 27 of 56 patients (48%) with variant angina studied with continuous electrocardiographic monitoring. In 23 of 27 patients, ventricular arrhythmias developed during maximal S-T segment elevation (occlusion arrhythmias) and in 10 during return of S-T segment to baseline (reperfusion arrhythmias). Patients with ventricular tachyarrhythmias did not differ from those without arrhythmias in regard to clinical, electrocardiographic, and angiographic findings. Both occlusion and reperfusion arrhythmias were correlated with the degree of S-T segment elevation; reperfusion arrhythmias were also related to the duration of acute ischemia. These data suggest that in variant angina, ventricular tachyarrhythmias may be triggered either by vasospastic coronary occlusion or by reperfusion after relief of spasm. Severity and duration of ischemia appear to be the main determinants of the arrhythmias, while clinical and angiographic characteristics are not good predictors of their presence.

26 **Long-Term Responses to Nifedipine in Patients With Coronary Spasm Who Have an Initial Favorable Response**

JAMES A. HILL, ROBERT L. FELDMAN, C. RICHARD CONTI, CAROL K. HILL, and CARL J. PEPINE

Fourteen patients with coronary spasm selected because of a good short-term (4 weeks) decrease in angina frequency with nifedipine were followed up for an average of 9.4 months. Of these patients, 12 (86%) had a continued good response (transient slight increase or no change), but 8 (67%) required therapy in addition to nifedipine (nitrates, beta blockers, surgery) to maintain angina control. In 5 patients (36%), nifedipine therapy was limited because of adverse effects. Three patients had unstable angina requiring hospitalization during this time. Patients with coronary spasm selected because of a favorable short-term reduction in angina frequency with nifedipine were effectively treated over the long term with nifedipine, but additional therapy was often needed to control symptoms. Adverse effects were common, but dose reduction usually diminished these effects.

30 **Prognostic Value of Resting and Submaximal Exercise Radionuclide Ventriculography After Acute Myocardial Infarction in High-Risk Patients With Single and Multivessel Disease**

PASCAL NICOD, JAMES R. CORBETT, BRIAN G. FIRTH, SAMUEL E. LEWIS, ROBERT E. RUDE, ROBERT HUXLEY, and JAMES T. WILLERSON

In patients who survive the acute phase of myocardial infarction, those with multivessel coronary artery disease generally have a worse prognosis than those with single-vessel disease. However, some with significant multivessel stenoses have a good prognosis, whereas some with a significant single-vessel stenosis have a poor prognosis. Other factors, including the degree of left ventricular dysfunction at rest, have an important bearing on prognosis. The present study suggests that functional alterations in radionuclide-determined left ventricular volumes and ejection fraction during submaximal exercise testing may be of more prognostic importance than the delineation of coronary arterial anatomy or the assessment of residual ventricular function at rest in this setting.

37 **Evaluation of a QRS Scoring System in Acute Myocardial Infarction: Relation to Infarct Size, Early Stage Left Ventricular Ejection Fraction, and Exercise Performance**

YOSHIHIKO SEINO, HOWARD M. STANILOFF, WILLIAM E. SHELL, DAVID MICKLE, PREDIMAN K. SHAH, and JOHN K. VYDEN

The quantitative values of the recently proposed QRS scoring system (QRSs) using a standard 12-lead electrocardiogram in the early stage of acute myocardial infarction (AMI) were evaluated in terms of (1) how the QRSs actually correlated with enzymatically estimated infarct size and left ventricular ejection fraction (LVEF) determined by multiple-gated equilibrium cardiac blood pool scintigraphy, and (2) the relation to exercise test results soon after AMI. QRSs significantly correlated with infarct size ($r = 0.72$) and LVEF ($r = -0.71$). Also, the QRSs significantly related to exercise tolerance, exercise symptoms, and exercise S-T changes. These data suggest that the QRSs in the early stage of AMI will be clinically useful not only as a variable that correlates with infarct size and LVEF, but also as an aid in early identification of exercise performance soon after AMI.

Continued on page A25

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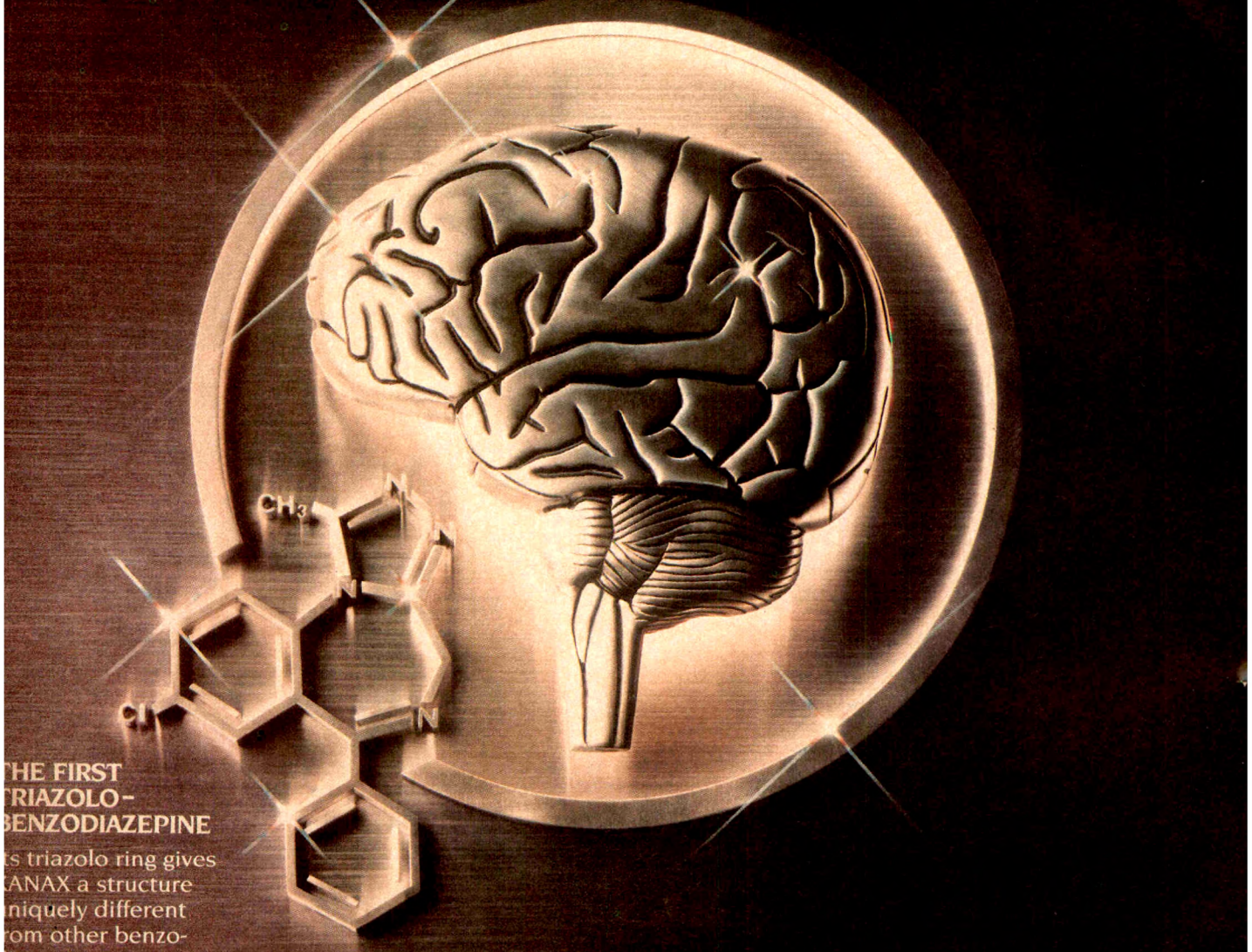

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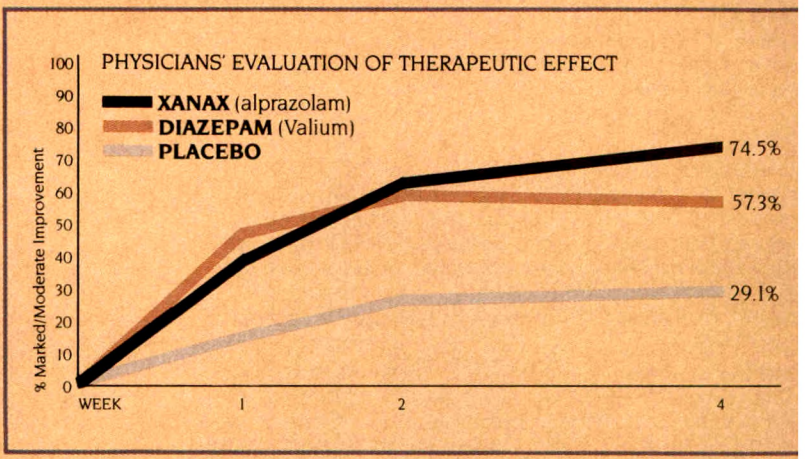
In double-blind, placebo-controlled clinical trials in 976 patients with moderate to severe clinical anxiety, therapy with XANAX was compared to diazepam (Valium).*

Patients treated with XANAX *had a significantly lower incidence of drowsiness when compared directly to diazepam* therapy (Valium) in *a 976-patient,* placebo-controlled, multicenter study.*

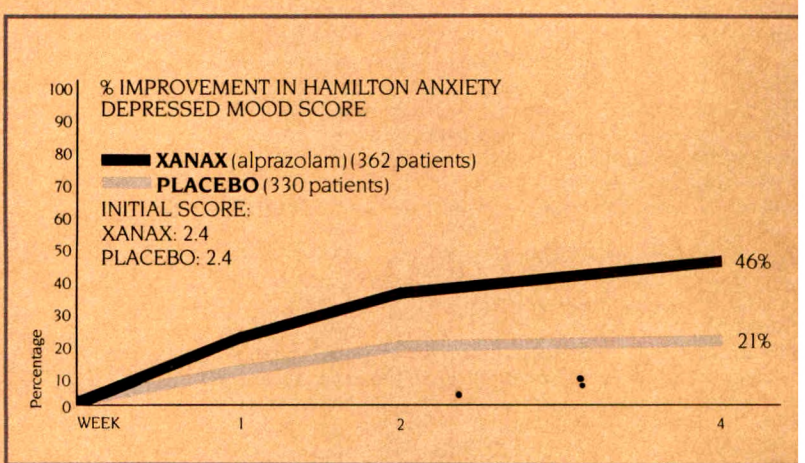


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOM

EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE:
XANAX 0.25–0.5 mg T.I.D.

The usual starting dose of XANAX is 0.25 to 0.5 mg, three times daily.

Please see next page for brief summary of prescribing information.

P 24, 134

Xanax® 0.5 mg Tablets
alprazolam Ⓒ

XANAX® Tablets ℞
(alprazolam)

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 42 (9):347-351, 1981.

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ANGIOGRAPHY 1983: Advances in Digital Imaging, Cardiovascular and Interventional Radiology. The Thirteenth Annual Postgraduate course will be held October 16–20, 1983 at the Hyatt Regency Cambridge. Didactic sessions will be devoted to specific organ areas, such as the genitourinary tract, the hepatobiliary tree, the gastrointestinal tract, and the peripheral vascular system. Symposia will be given on technical and procedural advances, such as new imaging modalities, digital imaging equipment and techniques, and interventional procedures. There will be one full day of small-group workshop sessions on specific areas, with optional workshops on the basics on Sunday evening. The Program Director is Michael A. Bettmann, M.D. The guest faculty includes Drs. Baum, Capp, Dotter, Dunnick, Millan, Sos and Widrich. The Harvard Medical School faculty includes Drs. Abrams, Bettmann, Clouse, Debrun, Fellows, Ferrucci, Harrington, Levin, Salzman, Waltman and others. The fee is $400; residents/fellows/RTs: $285. Approximately 28 hours of Category I credit can be obtained. For further information contact: Department of Continuing Education, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115.

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43 Multiform Accelerated Idioventricular Rhythm in Acute Myocardial Infarction: Electrocardiographic Characteristics and Response to Verapamil

SAMUEL SCLAROVSKY, BORIS STRASBERG, JACOB FUCHS, RUBEN F. LEWIN, ALEXANDER ARDITI, ELIEZER KLAINMAN, OSCAR H. KRACOFF, and JACOB AGMON

This study describes 13 patients with acute myocardial infarction in whom multiform accelerated idioventricular rhythm (AIVR) developed. In all patients the arrhythmia was intermittent and benign, caused no hemodynamic compromise, and was not associated with serious ventricular arrhythmias. Multiform AIVR with 2 morphologies was detected in 7 cases, with 3 morphologies in 5 cases, and with 4 morphologies in 1 case. Intravenous verapamil was given in 6 patients. It caused no change in the rate of AIVR in 1 patient, decreased the rate of AIVR by 20 beats/min in 1 patient and abolished the arrhythmia in 4 patients.

48 Subcostal 2-Dimensional Echocardiographic Imaging of Peripheral Left Coronary Artery Aneurysms in Kawasaki Disease

TOSHIKI MAEDA, HITOSHI YOSHIDA, TAKASHI FUNABASHI, SHIGEKAZU NAKAYA, SHOJI TAKABATAKE, TAKASHI OHNO, and NOBORU TANIGUCHI

Coronary aneurysm is an ominous complication of Kawasaki disease associated with a risk of sudden death. Two-dimensional (2-D) echocardiography can be used to visualize coronary aneurysms with use of the parasternal horizontal approach at the level of the aorta. However, this approach visualizes only limited areas of the proximal segments of the coronary arteries. A previous study provided a 2-D echocardiographic technique to detect peripheral right coronary aneurysms using the subcostal approach. An additional study was performed to detect peripheral coronary aneurysms of the left coronary artery from the ostium to terminal sites in both left anterior descending and left circumflex arteries, using the subcostal approach. In this study, 3 aneurysms at the origin of the obtuse marginal artery (1 in segment 13 and 2 at the origin of the second diagonal branch) were visualized with 2-D echocardiography. These echocardiographic studies were done prospectively and their features coincided well in size, shape, and anatomic location with confirmatory angiographic appearances.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

55 Prolongation of the Q-T Interval in Man During Sleep

KEVIN F. BROWNE, ERIC PRYSTOWSKY, JAMES J. HEGER, DONALD A. CHILSON, and DOUGLAS P. ZIPES

Parasympathetic blockade shortens the duration of the Q-T interval and ventricular effective refractory period independent of heart rate change. Since relative parasympathetic effect increases during sleep, it was determined whether sleep was associated with a change in the Q-T interval. Fifteen patients receiving no drugs underwent 3 to 6 days of continuous electrocardiographic recording. Comparison of R-R intervals that had similar durations during sleep and awake states revealed that the duration of the Q-T interval was longer during sleep in all 15 patients. Comparison of linear regression lines in 8 patients who had a sufficient range of overlap of R-R intervals demonstrated that the regression lines during sleep were significantly different from those during the awake state. The difference in the Q-T interval between awake and sleeping states was 19 ± 7 ms when calculated at a heart rate of 60 beats/min. These statistical comparisons of the Q-T and R-R intervals indicate that the Q-T interval is longer during sleep than awake state at the same heart rate. Prolongation of the Q-T interval during sleep may reflect increased parasympathetic tone or sympathetic withdrawal. These changes in repolarization may be related to the diurnal variation of some ventricular arrhythmias.

60 Relation of Mode of Induction and Cycle Length of Ventricular Tachycardia: Analysis of 104 Patients

JOHN U. DOHERTY, MICHAEL G. KIENZLE, HARVEY L. WAXMAN, ALFRED E. BUXTON, FRANCIS E. MARCHLINSKI, and MARK E. JOSEPHSON

In 104 patients with ventricular tachycardia (VT), the cycle length (CL) was correlated with the mode of initiation (single, double, and triple extrastimuli and rapid pacing). VT induced with a single extrastimulus was slower (342 ± 72 ms, mean CL) than that induced with double (295 ± 60 ms) or triple (282 ± 56 ms) extrastimuli or rapid pacing (293 ± 40 ms). There was no difference among the last 3 groups. Thirty-eight patients had endocardial catheter mapping, and the distance between site of stimulation and origin of VT was determined. There was no difference in mode of initiation when the stimulation site was close, intermediate, or distant from the site of origin. Mode of initiation was also correlated with site of previous myocardial infarction in 69 patients initiated from the right ventricular apex. Mode of initiation did not differ among patients with septal, inferior, lateral, or multiple myocardial infarctions. Thus, the CL of VT initiated with a single extrastimulus was slower than that initiated with double or triple extrastimuli or rapid pacing, and the mode of initiation was unrelated to the site of previous myocardial infarction or to the distance between stimulation site and site of origin of VT.

Continued on page A29

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DESCRIPTION: Nitrodisc incorporates a patented Microseal Drug Delivery™ system consisting of a solid, nitroglycerin-impregnated polymer bonded to a flexible, non-sensitizing adhesive bandage. It is designed to be applied topically. Nitrodisc provides constant and controlled drug delivery over a uniform skin surface area for 24 hours.

Nitrodisc is available in two strengths which release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system contains 16 mg nitroglycerin over an 8 cm^2 releasing surface. The 10 mg/24 hr system contains 32 mg nitroglycerin over a 16 cm^2 releasing surface.

INDICATIONS AND USAGE: Nitrodisc is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Nitrodisc (nitroglycerin) is contraindicated in patients known to be intolerant of organic nitrate drugs, and in patients with marked anemia, increased intraocular pressure, or increased intracranial pressure.

WARNINGS: In patients with acute myocardial infarction or congestive heart failure, Nitrodisc should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent potential withdrawal reactions, which are characteristic of all vasodilators in the nitrate class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitrodisc is not intended for immediate relief of anginal attacks. For this purpose, occasional use of sublingual preparations may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Nitrodisc therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, Nitrodisc (nitroglycerin) dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION: Nitrodisc should be applied once each day. To use Nitrodisc, follow the instructions on the package. Nitrodisc should be applied to an intact skin site free of hair and not subject to excessive movement. It should not be applied to the distal parts of the extremities. A suitable area should be shaved free of hair, if necessary. The application site should be changed slightly each time to avoid undue skin irritation. A new Nitrodisc should be applied if the product loosens.

The optimal dosage regimen should be selected based upon the clinical response, the side effects, and the effects of therapy upon blood pressure and heart rate. It is recommended that therapy be initiated with the smaller Nitrodisc, and that the larger Nitrodisc be utilized when a greater response is desired. In the event that higher doses are necessary, multiple pads may be applied.

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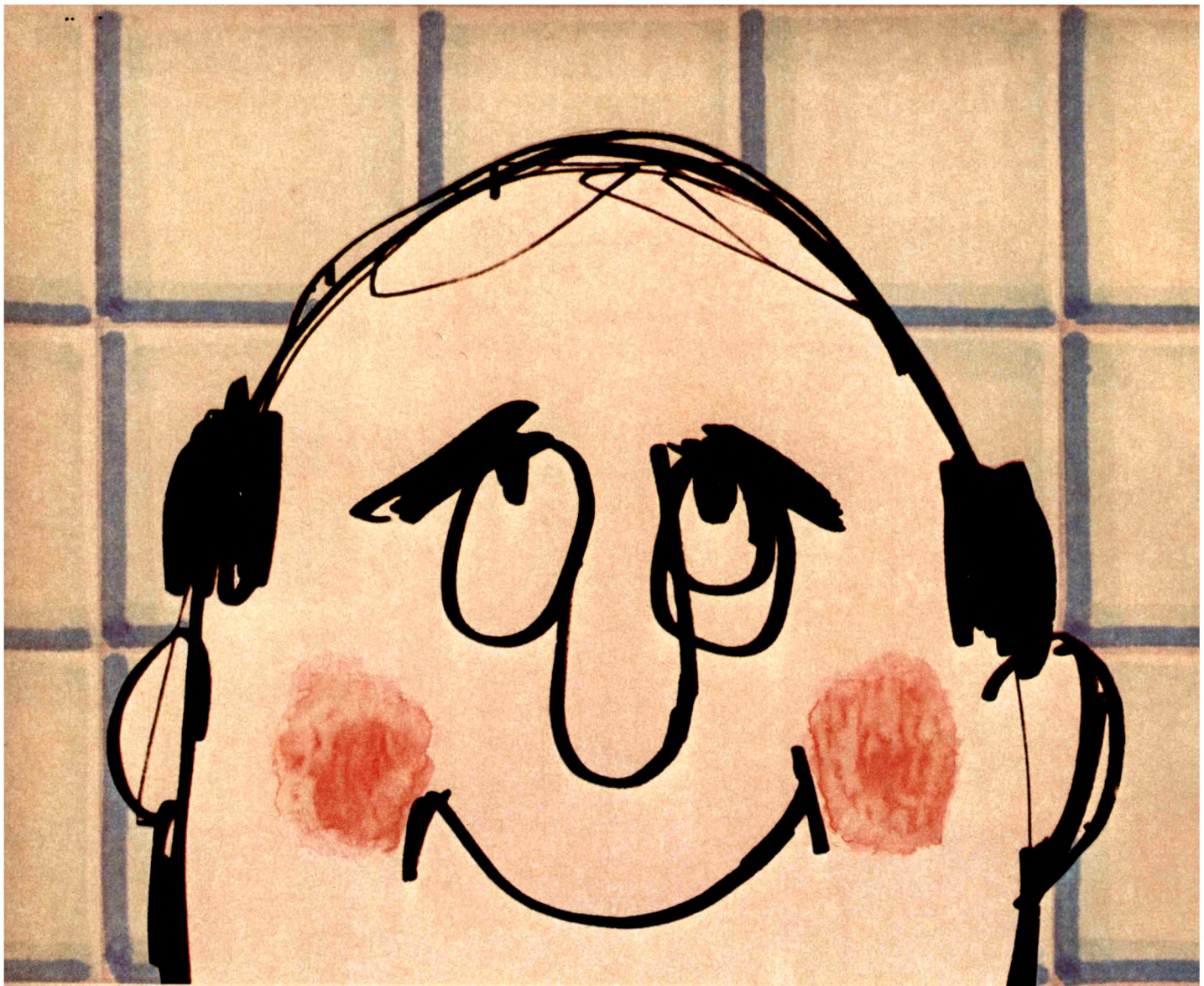

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CONTENTS

65 Cardiac Arrest in Young, Ostensibly Healthy Patients: Clinical, Hemodynamic, and Electrophysiologic Findings

D. WOODROW BENSON, Jr., DAVID G. BENDITT, ROBERT W. ANDERSON, ANN DUNNIGAN, MARC R. PRITZKER, THOMAS J. KULIK, and JAMES H. ZAVORAL

This study examines the clinical, hemodynamic, and electrophysiologic findings in a unique group of 11 young (aged 15 months to 29 years) survivors of cardiac arrest. All patients were previously in good health, and cardiac arrest was the initial manifestation of cardiac disease. Overt clinical and hemodynamic abnormalities were not as common as previously reported, and in some instances apparent cardiac abnormalities failed to provide a link to cardiac arrest. However, during multicatheter electrophysiologic study, sustained tachyarrhythmia was reproducibly initiated in 8 of 11 patients (73%). Treatment to prevent recurrence of cardiac arrest was difficult in this group of patients.

70 Value of the Ajmaline-Procainamide Test to Predict the Effect of Long-Term Oral Amiodarone on the Anterograde Effective Refractory Period of the Accessory Pathway in the Wolff-Parkinson-White Syndrome

PEDRO BRUGADA, WILLEM R. DASSEN, SIMON BRAAT, ANTON P. GORGELS, and HEIN J. J. WELLENS

A retrospective study was undertaken in 36 patients with the Wolff-Parkinson-White (WPW) syndrome to assess the value of an ajmaline/procainamide test to predict the effect of chronic oral amiodarone on the duration of the anterograde effective refractory period (ANT ERP) of the accessory pathway. Before amiodarone, in 24 patients (group A) ajmaline (24 patients) (50 mg intravenously over 3 minutes) or procainamide (11 patients) (10 mg/kg body weight intravenously over 10 minutes) failed to block anterograde conduction over the accessory pathway during sinus rhythm (a negative ajmaline/procainamide test). In 12 patients (group B), ajmaline (12 patients) or procainamide (7 patients) blocked anterograde conduction over the accessory pathway during sinus rhythm (a positive test). The two groups differed in the duration of the ANT-ERP of the accessory pathway measured at control study (237 ± 24 ms in group A and 284 ± 25 ms in group B, $p < 0.05$). After oral amiodarone (total dose 8,400 to 11,200 mg over 4 to 6 weeks), 83% of the patients in group A had an ANT-ERP of the accessory pathway of 260 to 330 ms and 83% of the patients in group B had an ANT-ERP of the accessory pathway of ≥330 ms ($p < 0.01$). Thus, ajmaline/procainamide testing performed before initiation of amiodarone therapy is of value in predicting the results of oral amiodarone on the duration of the ANT-ERP of the accessory pathway in the WPW syndrome.

73 Evaluation of Metoprolol in Suppressing Complex Ventricular Arrhythmias

CRAIG M. PRATT, SHEILA C. YEPSEN, M. G. KIM BLOOM, ADDISON A. TAYLOR, JAMES B. YOUNG, and MIGUEL A. QUINONES

Twenty patients with cardiac disease and complex ventricular ectopy were studied using a placebo-controlled, single-blind protocol (3-day placebo; 3-day metoprolol, 100 mg/day; 4-day metoprolol, 200 mg/day) and continuous ambulatory electrocardiographic monitoring. Although high-dose metoprolol suppressed only 60% of all premature ventricular beats, it was increasingly effective in suppressing pairs and ventricular tachycardia (84 and 94% suppression, respectively). The mean plasma peak metoprolol levels to achieve this reduction was 72 ± 34 ng/ml. At this plasma metoprolol level, beta blockade was demonstrated by a decrease in mean 24-hour heart rate during normal activity from 78 ± 8 to 62 ± 4 beats/min ($p < 0.001$). While the resting left ventricular ejection fraction was unaffected by this plasma metoprolol level, pulmonary function including forced expiratory volume and forced vital capacity was significantly reduced, but returned to normal with metaproterenol.

79 Syncope and Ventricular Tachycardia in Patients With Ventricular Preexcitation

ELWYN A. LLOYD, RICHARD N. HAUER, DOUGLAS P. ZIPES, JAMES J. HEGER, and ERIC N. PRYSTOWSKY

Patients with the Wolff-Parkinson-White syndrome may have syncope caused by arrhythmias involving the accessory pathway: for example, atrioventricular reentrant tachycardia at a rapid rate or atrial fibrillation with a fast ventricular response due to conduction over the accessory pathway. However, these patients are not exempt from other causes of syncope. Four patients with ventricular preexcitation are presented whose syncope was initially attributed to an arrhythmia utilizing the accessory pathway. At electrophysiologic study, the electrophysiologic properties of the accessory pathways were considered unlikely to support tachycardia of a rate sufficient to result in syncope, but ventricular tachycardia was induced in all patients and was thought to be the cause of syncope in 3.

Continued on page A33

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[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after **abrupt** discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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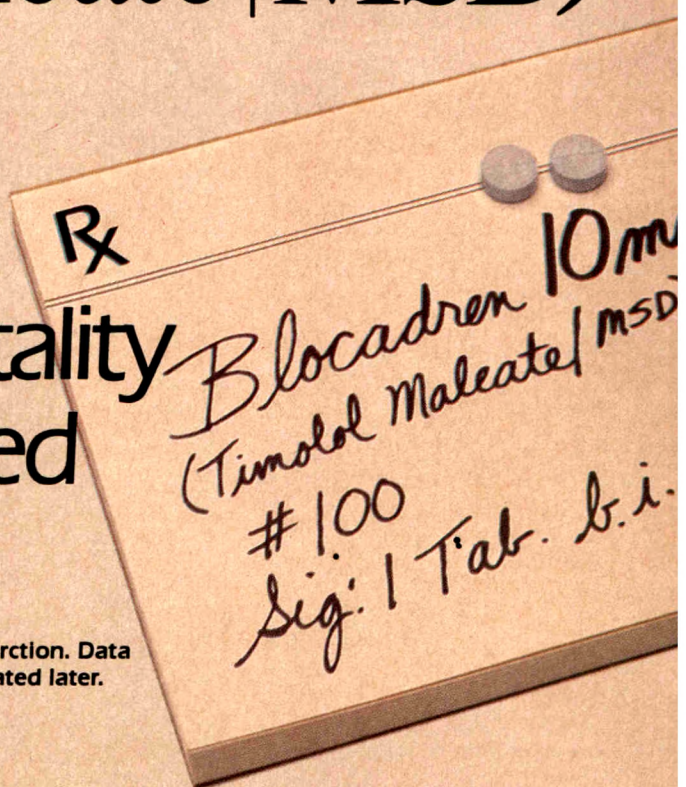

Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.

disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: *Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.
‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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CONTENTS

83 Efficacy, Safety, and Pharmacokinetics of a Concentration-Maintaining Regimen of Intravenous Pirmenol

MICHAEL J. REITER, STEPHEN C. HAMMILL, DAVID G. SHAND, CHAKO VERGHESE, ELIZABETH McCARTHY, and EDWARD L. C. PRITCHETT

A 3-stage, concentration-maintaining intravenous infusion regimen of pirmenol was tested for efficacy and safety in 8 subjects with chronic, stable premature ventricular beats. The regimen maintained stable plasma pirmenol levels of 0.94 to 2.75 mg/ml during infusions lasting up to 48 hours. In randomized, double-blind, placebo-controlled studies in 5 patients, pirmenol suppressed average premature ventricular beat frequency 93 ± 6% compared with control values. Pirmenol infusions were unassociated with adverse effects or toxicity. Pirmenol is therefore considered a promising antiarrhythmic agent.

88 Current Physiologic Pacemakers: A Serious Problem With a New Device

JOSEPH W. RUBIN, MARTIN J. FRANK, JOHN P. BOINEAU, and ROBERT G. ELLISON

This report describes the early results of treatment of symptomatic bradyarrhythmias in 20 patients with an automatic (DDD) pacemaker (Medtronic model 7000, Versatrax I). Nine patients had optimal DDD-mode pacing during 78 paced months. In 3 patients, the DDD mode was changed to atrioventricular sequential (DVI) early because of risk imposed by sustained tachycardia upon underlying myocardial ischemia. The other 8 had sustained tachycardia due to pacemaker reentry, and 7 developed neurologic and cardiovascular symptoms. DDD pacing was abandoned in 5 when reentry could not be interrupted by digitalis administration or reprogramming. Three continue to be paced in the DDD mode despite intermittent reentrant tachycardias; digitalis diminishes episodes of reentry in only 1. Reentrant tachycardia caused by the occurrence of slow retrograde atrioventricular conduction combined with a short, fixed atrial refractory period renders this pacemaker unsatisfactory for DDD-mode pacing in many patients.

92 Left Ventricular Function at Rest and During Exercise in Congenital Complete Heart Block: A Radionuclide Angiographic Evaluation

BRUNO V. MANNO, A-HAMID HAKKI, ESHAGH ESHAGHPOUR, and ABDULMASSIH S. ISKANDRIAN

Left ventricular function and volume were evaluated at rest and during upright exercise in 5 patients with congenital complete heart block by means of radionuclide ventriculography. Resting cardiac output was maintained at a normal level by an increase in end-diastolic volume rather than a decrease in end-systolic volume. The left ventricular ejection fraction was normal at rest in all patients but an abnormal response to exercise was noted in 3 patients. Thus, patients with congenital complete heart block utilize the Starling mechanism to maintain normal resting cardiac output, but the left ventricular response to exercise is usually abnormal even in the absence of symptoms.

95 Idiopathic Paroxysmal Ventricular Tachycardia With a QRS Pattern of Right Bundle Branch Block and Left Axis Deviation: A Unique Clinical Entity With Specific Properties

FUN-CHUNG LIN, C. DAVID FINLEY, SHAHBUDIN H. RAHIMTOOLA, and DELON WU

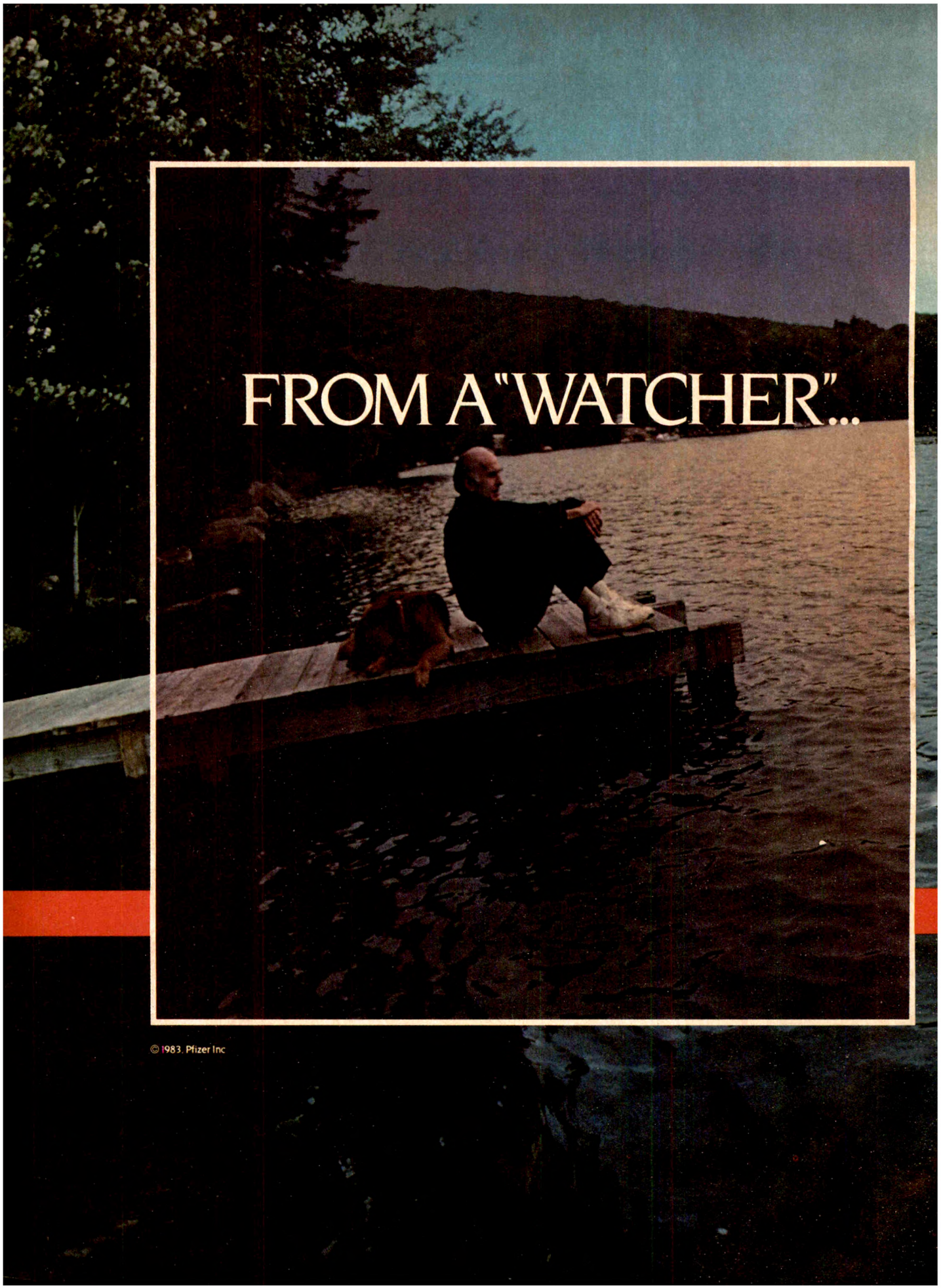
A distinct entity of recurrent, sustained ventricular tachycardia is reported in 4 young, asymptomatic patients without obvious heart disease. In these patients, the electrocardiogram during sinus rhythm showed a repolarization abnormality over inferior and lateral precordial leads. During tachycardia, the electrocardiogram showed a QRS pattern of right bundle branch block and left axis deviation. The tachycardia was inducible with electrical stimulation, highly responsive to verapamil, partially responsive to procainamide, and nonresponsive to lidocaine and propranolol.

CONGESTIVE HEART FAILURE

101 Platelet Alpha$_2$ Adrenoreceptors in Chronic Congestive Heart Failure

ROBERT J. WEISS, MICHAEL TOBES, CURTIS E. WERTZ, and CHARLES B. SMITH

Patients with chronic congestive heart failure (CHF) have elevated levels of circulating norepinephrine. The alpha$_2$ adrenoreceptor located on noradrenergic neurons exerts a negative feedback on the release of norepinephrine. This receptor is also located on human blood platelets. The present study compared the specific binding of ^{3}H-clonidine and ^{3}H-yohimbine to alpha$_2$ adrenoreceptors in platelet membranes isolated from normal persons and patients with class I and II and class III and IV CHF. A significant decrease in receptor number was found between normal volunteers and patients with class III and IV CHF (^{3}H-clonidine 25%, $p < 0.05$; ^{3}H-yohimbine 43%, $p < 0.005$). These results support the hypothesis that increased concentrations of circulating norepinephrine lead to a decrease in platelet alpha$_2$ adrenoreceptors. Such changes in receptor number may prove valuable in monitoring therapy of patients with CHF.



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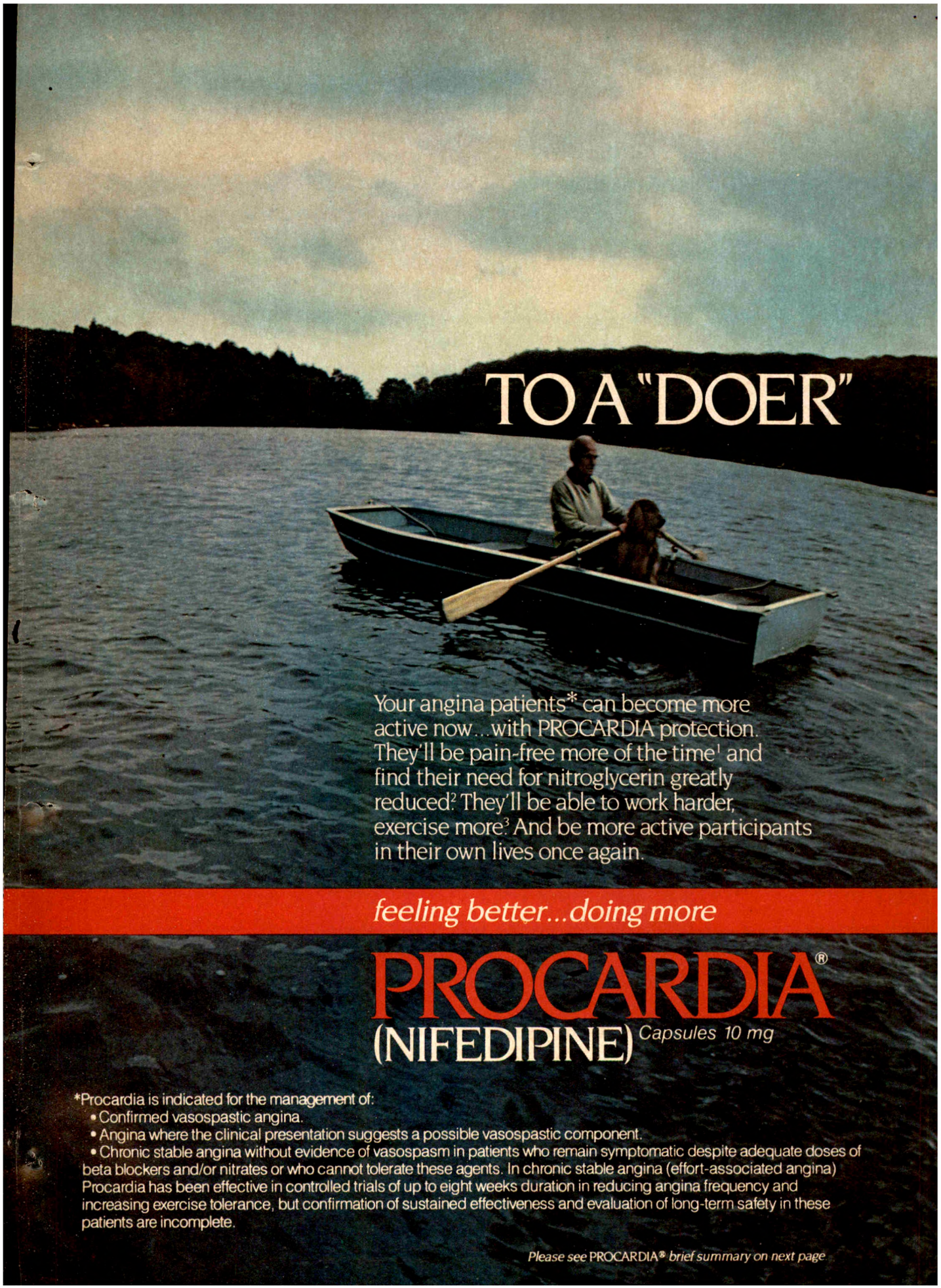
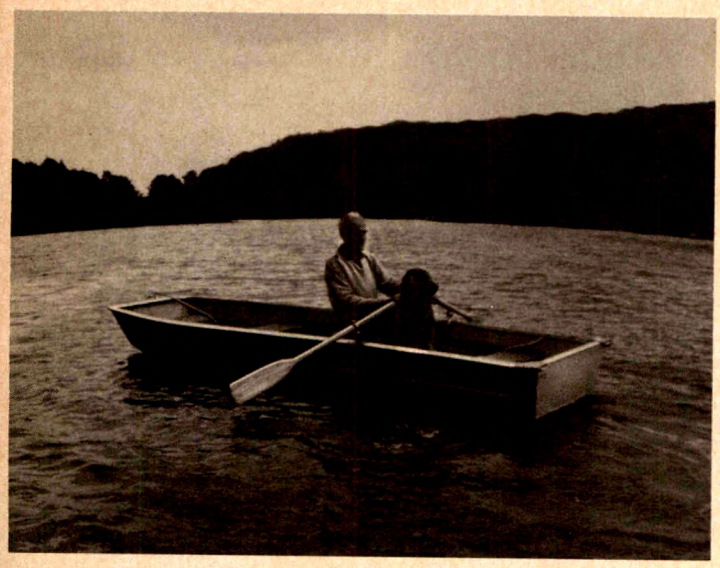


*Procardia is indicated for the management of:

- Confirmed vasospastic angina.
- Angina where the clinical presentation suggests a possible vasospastic component.
- Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) Procardia has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA® *brief summary on next page*

feeling better...doing more



PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

–Usual effective dosage is 30-60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

–Offers a favorable safety profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302: 1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.

BRIEF SUMMARY
PROCARDIA® CAPSULES
(nifedipine)
For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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Another reason we're called PACE*SETTER:*

The dual-personality pacing therapy system.

Introducing a total pacing therapy system with *one* ultra-sophisticated programmer/telemetry unit compatible with both single-chamber and *dual*-chamber pacemakers.

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The Pacesetter*® *Model 398E Programming/Telemetry System.
Multi-programmability up to six parameters; extensive programmed and measured telemetry data capable of advising physicians both what the pacing system *should* be doing as well as what it is *actually* doing.

Printout indicates extensive telemetered information. Programmer face displays full menu of programmable parameters and values possible.

Pacesetter® Systems, Inc.

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CONGENITAL HEART DISEASE

106 Cardiovascular Effects of Breathing 95 Percent Oxygen in Children With Congenital Heart Dis

ROBERT H. BEEKMAN, ALBERT P. ROCCHINI, and AMNON ROSENTHAL

The hemodynamic effects of breathing 95% oxygen were evaluated in 26 children with congenita ease. After 10 minutes of breathing 95% oxygen, arterial oxygen partial pressure increased from 8 420 ± 89 torr ($p < 0.001$). Cardiac index decreased 21% from 3.96 ± 0.94 to 3.12 ± 0.74 liters/ < 0.001), and stroke index decreased by 11% ($p < 0.001$). A 23% decrease in oxygen consumption (was observed, and oxygen transport decreased from 672.9 ± 179.4 to 600.2 ± 161.3 ml O_2/min/m^2 (Heart rate was kept constant by atrial pacing in a second group of 5 patients; 95% oxygen still signif creased cardiac index, oxygen consumption and stroke index.

112 Altered Baroreceptor Function in Children With Systolic Hypertension After Coarctation Repai

ROBERT H. BEEKMAN, BARRY P. KATZ, CATHERINE MOOREHEAD-STEFFENS, and ALBERT P. ROCCHINI

Baroreceptor function was evaluated in 6 children with repaired coarctation of the aorta with mild ar hypertension and compared with that in 7 normotensive control children. At catheterization, steady moidal baroreceptor function curves relating mean arterial pressure to R-R interval were derived by and decreasing mean arterial pressure with small injections of phenylephrine and nitroprusside. Com control children, the baroreceptor function curves of children with repaired coarctation of the aorta (1 about a higher baseline mean arterial pressure, (2) have a decreased slope, and (3) have a diminished val range.

118 Two-Dimensional Echocardiographic Assessment of Caval and Pulmonary Venous Pathways A Senning Operation

ALVIN J. CHIN, STEPHEN P. SANDERS, ROBERTA G. WILLIAMS, PETER LANG, WILLIAM I. NORWOOD, and ALDO R. CASTANEDA

Two-dimensional echocardiography was performed in 28 patients who had undergone the Senning p Normal values for the caval and pulmonary venous pathway dimensions are established from measur the 18 patients who had no caval or pulmonary venous obstruction or tricuspid regurgitation at cardiac ization. All patients with catheterization-proved caval or pulmonary venous obstruction or severe tricus gitation had echocardiographic dimensions outside this range. Two-dimensional echocardiography ca both quantitative and qualitative information about the caval and pulmonary venous pathways after th procedure.

127 Computer Interpretation of Pediatric Frank Vectorcardiograms in the Evaluation of Congenital Disease

CHRISTIAN R. BROHET, CHRISTIANE DERWAEL-BARCHY, ANNIE ROBERT, ROBERT FESLER, MADY STYNS, LUCIEN A. BRASSEUR, and ANDRÉ VLIERS

A new computer program for automatic interpretation of pediatric vectorcardiograms was tested in a 728 catheterized patients against the true clinical diagnosis determined from hemodynamic and ang data. The diagnostic accuracy (defined as the number of true-positive results plus true-negative resul by the total) was 78% for left ventricular hypertrophy, 79% for right ventricular hypertrophy, 84% fo cular hypertrophy, and 84% for "normal." In general, the accuracy of a positive diagnosis of any ab especially biventricular hypertrophy, was higher in children <2 years of age because of the higher pr of abnormal records in this age group. Thus, although the diagnostic performance of the current vers program was satisfactory, further improvement is expected by making the criteria more adaptable to th tion analyzed.

133 Glucose and Insulin Changes in Infants and Children Undergoing Hypothermic Open-Heart Surg

GEORGE BENZING III, PAUL D. FRANCIS, SAMUEL KAPLAN, JAMES A. HELMSWORTH, and MARK A. SPERLING

This study demonstrates that hyperglycemia, especially in smaller children, is related to excessive e glucose administration intraoperatively and low insulin levels. Since hyperglycemia and resultant osmo sis may give a false impression of cardiorenal performance postoperatively, its prevention has merit. R of glucose in the heart-lung priming solution and in the intraoperative intravenous solutions can preve glycemia.

Continued on page A46

Announcing a major advance
in cardiovascular therapy

New CARDIZEM™ (diltiazem HCl)

CALCIUM CHANNEL BLOCKADE

from Marion Laboratories

Potent coronary vasodilation with a distinctive hemodynamic profile

Please see full prescribing information on last pa

30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY WITH A LOW INCIDENCE OF SIDE EFFECTS

CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

These changes provide effective therapy with a low incidence of side effects.

Indications

(1) Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm.

(2) Cardizem is indicated in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

ANTIANGINAL MECHANISM OF ACTION

- Produces relaxation of coronary vascular smooth muscle
- Dilates both large and small coronary arteries at drug levels that cause little or no negative inotropic effect
- Produces dose-dependent decreases in peripheral resistance
- Resting heart rate is usually unchanged or slightly reduced

Reduces the pressure/rate product for any given work load in patients with effort-associated angina

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CARDIZEM™ (diltiazem HCl) offers a distinctive profile of effects

(1) Vascular smooth-muscle relaxation with a potent effect on the coronary arteries.[1]

(2) Mild effect on afterload reduction.

(3) In normotensive patients at rest, recommended dosage levels producing coronary vasodilation result in only a mild reduction in diastolic blood pressure and no change in heart rate.

(4) At submaximal exercise, it causes a reduction in heart rate and mean blood pressure compared with placebo, thus reducing myocardial oxygen demand and permitting patients to exercise significantly longer.

(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction.[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function.[3]

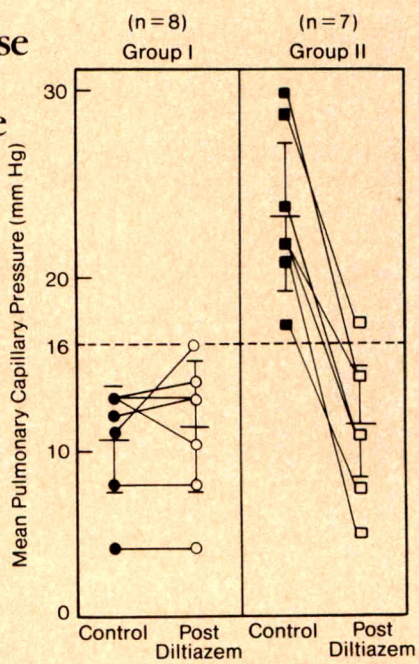
While Cardizem tends to prolong AV conduction,* only rarely has there been an increase in PR intervals outside of normal limits.

*See Contraindications and Warnings.

CARDIZEM™ (diltiazem HCl) tends to normalize stress-induced increases in pulmonary capillary pressure (PCP)

The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina.[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.



CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]

Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

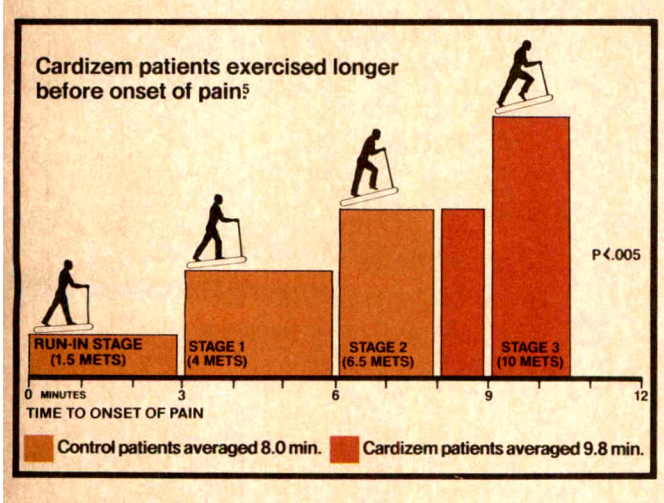
REFERENCES:

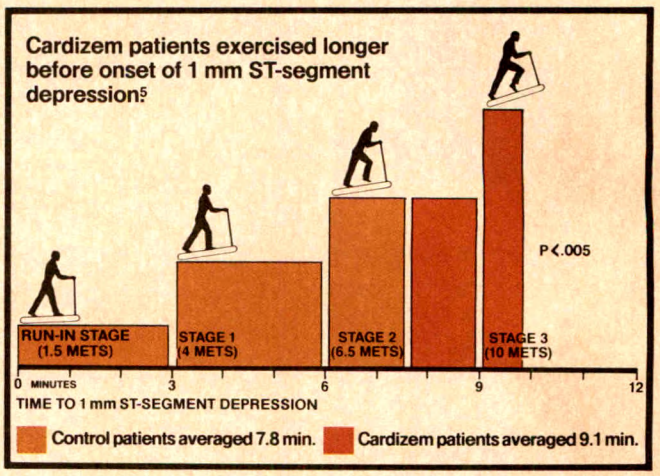
1. Rosenthal SJ, Ginsburg R, Lamb IH, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. *Am J Cardiol* 46:1027-1032, 1980.
2. Low RI, Takeda P, Lee G, et al: Effects of diltiazem-induced calcium blockade upon exercise capacity in effort angina due to chronic coronary artery disease. *Am Heart J* 101:713-718, 1981.
3. Wagner JM, Anderson JL, Bray BE, et al: Comparative effects of diltiazem, propranolol and placebo using exercise radionuclide ventriculography. Presented at American Heart Association meeting, Dallas, TX, Nov 1982. Abstracted, *Circulation* 66:11-22, 1982.
4. Hossack KF, Bruce RA, Ritterman JB, et al: Divergent effects of diltiazem in patients with exertional angina. *Am J Cardiol* 49:538-546, 1982.

Please see full prescribing information on last page of this ad.

EXCELLENT CLINICAL RESPONSE TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*





Protocol:

A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

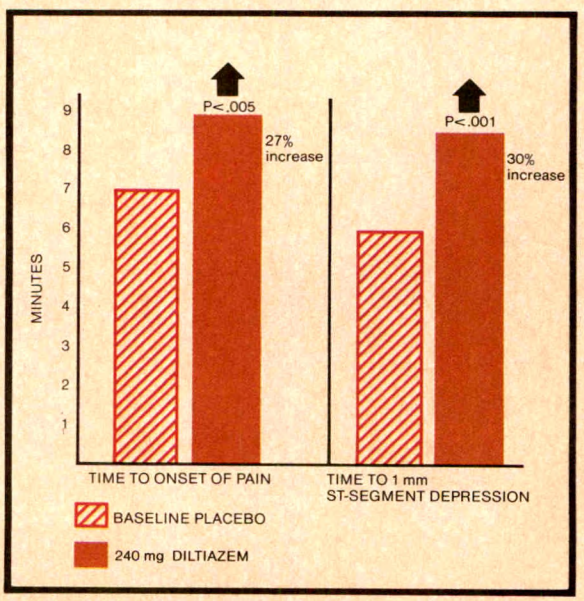
The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.

5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.
6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.

*This study is a report from one center in a multicenter study.

CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression



RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY.[6]

CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

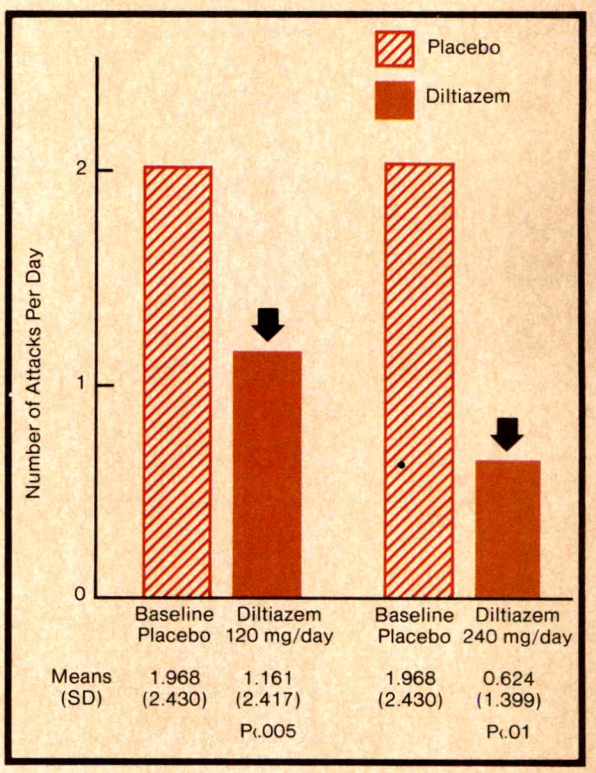
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]

71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]



7. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. *Am J Cardiol* 49:560-566, 1982.
8. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.
9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.

Please see full prescribing information on last page of this ad

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

LOW INCIDENCE OF SIDE EFFECTS WITH CARDIZEM™ (diltiazem HCl)

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

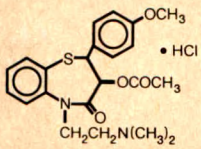
In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

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1/83

CARDIOMYOPATHY

137 Cardiac Amyloidosis Causing Cardiac Dysfunction: Analysis of 54 Necropsy Patients

WILLIAM C. ROBERTS and BRUCE F. WALLER

Clinical and morphologic findings are described in 54 necropsy patients (32 men [59%]) aged 21 to 97 years (mean 64) with cardiac amyloid deposits extensive enough to cause fatal cardiac dysfunction. Chronic congestive heart failure (CHF) was present in 46 (85%). The duration of CHF, known in 39 patients, ranged from 1 to 108 months (mean 18) and lasted ≤12 months in 25 patients (64%). All 8 patients without CHF died suddenly and unexpectedly. Systemic arterial pressures were recorded in the last 3 months of life in 43 patients; the peak indirect systolic pressure was ≤130 mm Hg and the diastolic pressure <90 mm Hg in all. Electrocardiograms, recorded in the last 6 months of life in 40 patients, were abnormal in each, revealing low voltage in 35 (63%); "myocardial infarction pattern" in 33 (83%); abnormal QRS axis in 29 (73%); arrhythmias in 29 (73%); first-, second-, or third-degree heart block in 28 (45%); and complete bundle branch block in 7 (18%). In 30 patients, the QRS amplitude in all 12 leads was measured. In the 15 men it ranged from 60 to 197 mm (mean 99) (10 mm = 1 mV) and in the 15 women from 58 to 199 mm (mean 109). The diagnosis of amyloidosis was established by biopsy of noncardiac organs or tissues during life in only 18 patients (33%). During life the condition simulated hypertrophic cardiomyopathy in 5 patients, constrictive pericardial disease in 3, and coronary heart disease (because of angina pectoris) in 4.

147 Cardiac Thrombosis and Thromboembolism in Chronic Chagas' Heart Disease

J. SAMUEL M. OLIVEIRA, ROSALLY R. CORREA DE ARAUJO, MARCOS A. NAVARRO, and GERSON MUCCILLO

A retrospective study of Chagas' heart disease was carried out by a review of 1,355 autopsy reports, with special reference to cardiac thrombus and thromboembolic phenomena. The incidence of cardiac thrombus was higher in cases of heart failure (36%) than in cases of sudden death (15%), higher in heavier hearts, and unrelated to age or sex. The left- and right-sided cardiac chambers were equally affected by thrombus. Endocarditis and blood stasis were considered important factors in the pathogenesis of cardiac thrombosis. Thromboembolic phenomena were more common in the systemic circulation but caused relatively more deaths by pulmonary embolism. Fourteen percent of the patients with thromboembolic phenomena actually died from them. Patients with multiple thromboembolic phenomena have a higher risk of death from embolism. Cardiac thrombosis or thromboembolic phenomena, or both, were present in 44% of the cases studied. Prophylactic measures should be taken for these important complications of Chagas' heart disease.

MISCELLANEOUS TOPICS

152 Aortic Valve Closure and Cardiac Vibrations in the Genesis of the Second Heart Sound

MARKKU KUPARI

Simultaneous M-mode echocardiograms and external phonocardiograms were recorded in 15 healthy subjects to evaluate the genesis of the second heart sound. The onset of the second sound was found synchronous with the coaptation of the aortic valve cusps and a sharp vibration on the aortic wall. The closed value was oscillating for 30 to 45 ms after the coaptation of the cusps. Magnified echocardiographic studies of the interventricular septum revealed a consistent, momentary quiver across the septal myocardium a mean of 4 ms after the onset of the second sound. In most subjects, a transient myocardial vibration was observed in temporal association with the first heart sound as well. These observations suggest that aortic valve closure initiates the production of the second heart sound; the main audible component results, however, from vibrations in the cardiac structures after valve closure.

155 Analysis of the Amount of Tricuspid Valve Anular Dilatation Required to Produce Functional Tricuspid Regurgitation

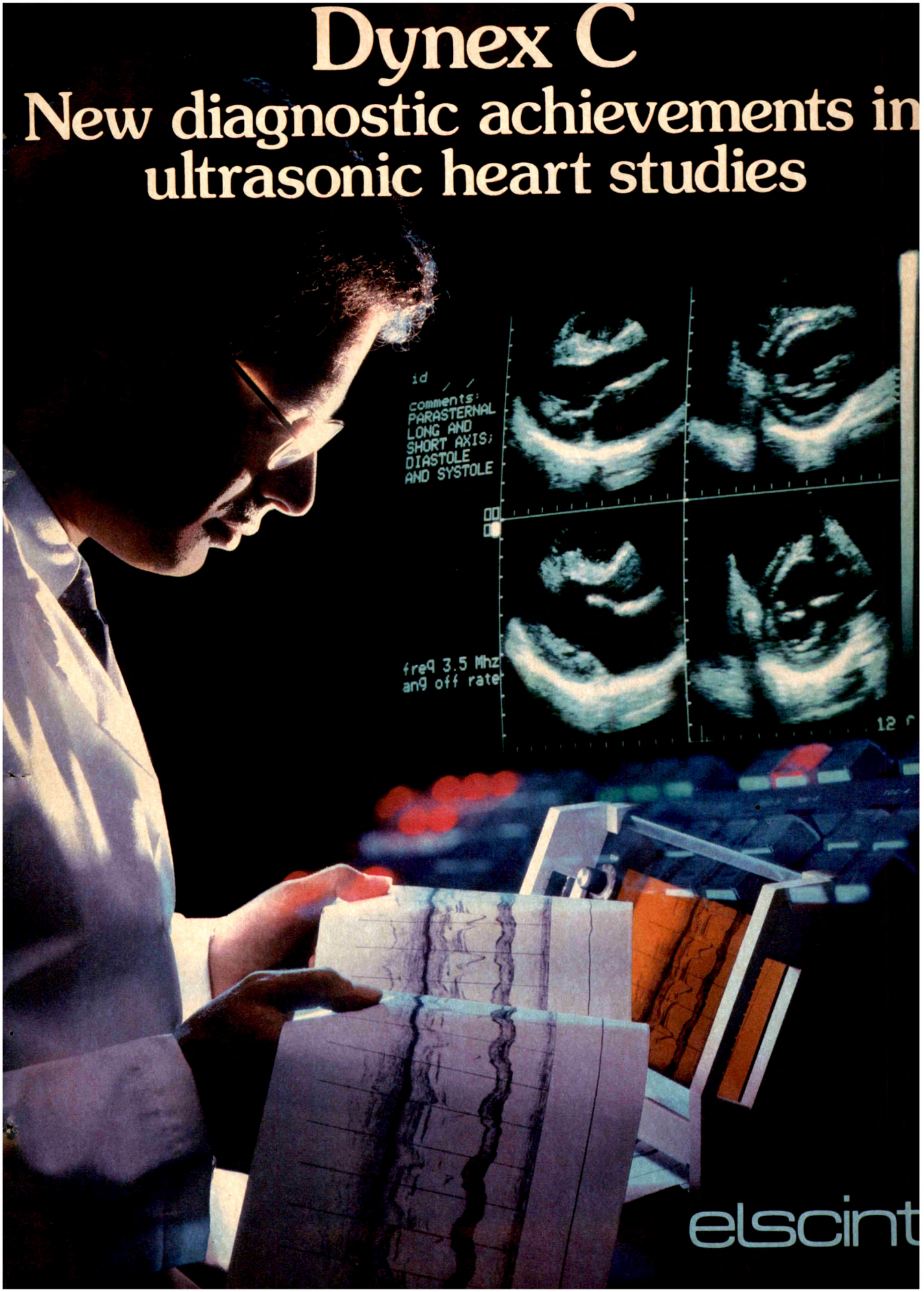
JOSE L. UBAGO, ALVARO FIGUEROA, ALBERTO OCHOTECO, THIERRY COLMAN, RAFAEL M. DURAN, and CARLOS G. DURAN

In an attempt to determine the critical anular dilatation required for functional tricuspid regurgitation (TR) and the role of the systolic anular shortening in the severity of this regurgitation, 67 patients with right ventriculography were studied. These patients were classified into Group I, control, and Group II, patients with rheumatic valvular disease. The 55 Group II patients were subclassified into Group IIa, patients without TR, Group IIb, patients with mild TR, and Group IIc, patients with moderate to severe TR. The angiographic maximal early systolic and minimal end-systolic diameters were measured. The shortening of the tricuspid anulus was expressed as percent reduction of the maximal diameter. The average maximal diameter in the control group was 21 ± 2 mm/m^2 and the minimal diameter 15 ± 2; the percent shortening was 30 ± 7%. The rheumatic patients had a larger maximal diameter than the control group. Anular shortening was reduced only in the group with moderate to severe

Continued on page A53

Dynex C

New diagnostic achievements in ultrasonic heart studies



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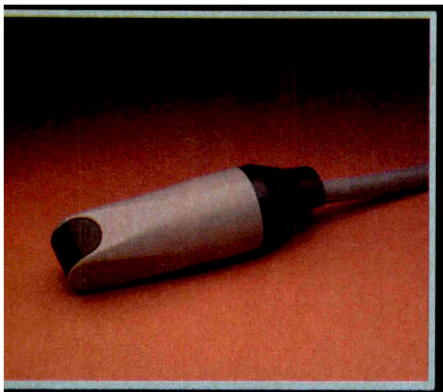
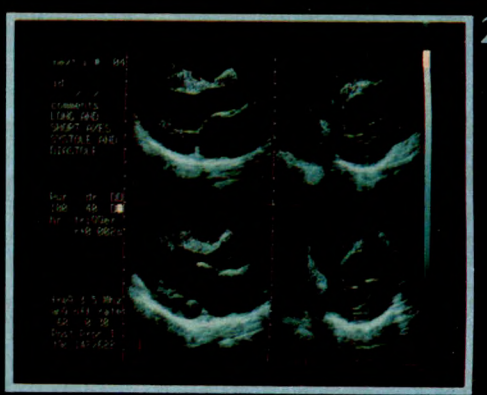


1. Dynex/C Probes: Out in Front

Dynex/C 3.5 and 5 MHz mechanical sector probes, feature four unique characteristics which put them far ahead of the field:

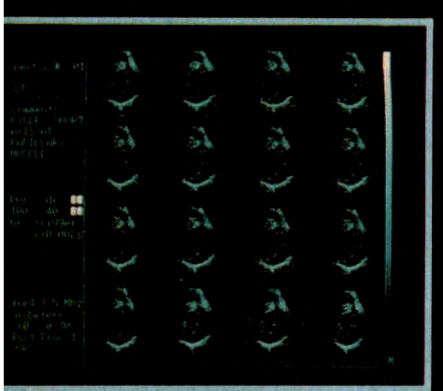
- □ Inherently fine spatial resolution due to computer controlled automatic line density optimization.
- □ An extremely wide, continuously variable 15-105° sector angle.
- □ Exceptionally fast frame rates: more than 70 frames per second, continuously variable.
- □ A continuously adjustable offset angle ranging from 0-45°.



2

Multiformatting: Comparison at a Glance

Dynex/C's ability to display four images simultaneously gives the cardiologist an incomparable diagnostic tool. He may compare four identical views taken over a period of time, or study four different images acquired during the same examination — for example, tomographic sections along the long and short axes, at end systole and end diastole.



3. CCRM™ — Cardiac Cycle Review Mode

The CCRM is an exclusive Dynex/C feature for viewing fast sequential 2-D cardiac events, or a complete heart cycle.

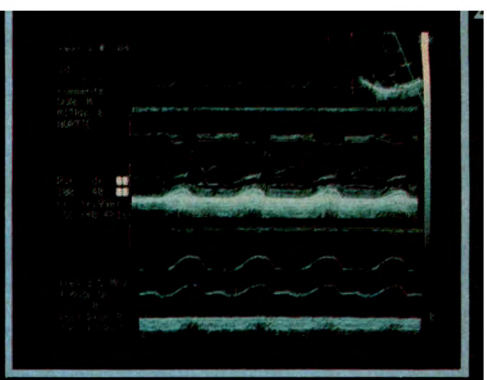
Cardiac scanning at an extremely fast frame rate stops at a pre-selected ECG point. The last 16 frames acquired are stored in memory, and may be reviewed separately or in closed-loop cine mode at a user-selected speed.

elscint

4. M-Mode Display Capabilities

Dynex/C's M-mode has two features of truly exceptional value to the cardiologist:

1. Simultaneously with normal M-mode, Dynex/C displays a two-dimensional image with M-mode position precisely defined by a cursor.
2. *Dual M-mode:* simultaneous display of two M-modes from different cardiac regions, both synchronized with a user-selected ECG or PCG point.



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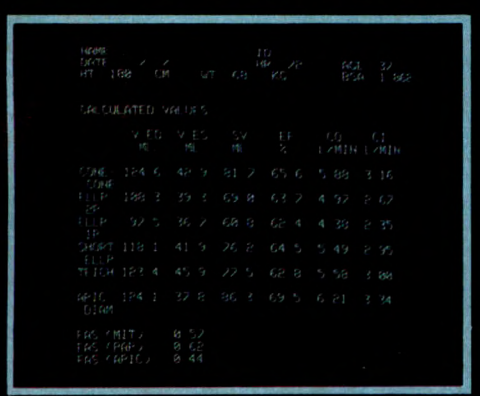
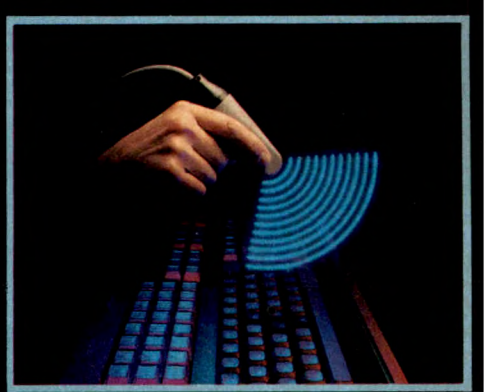


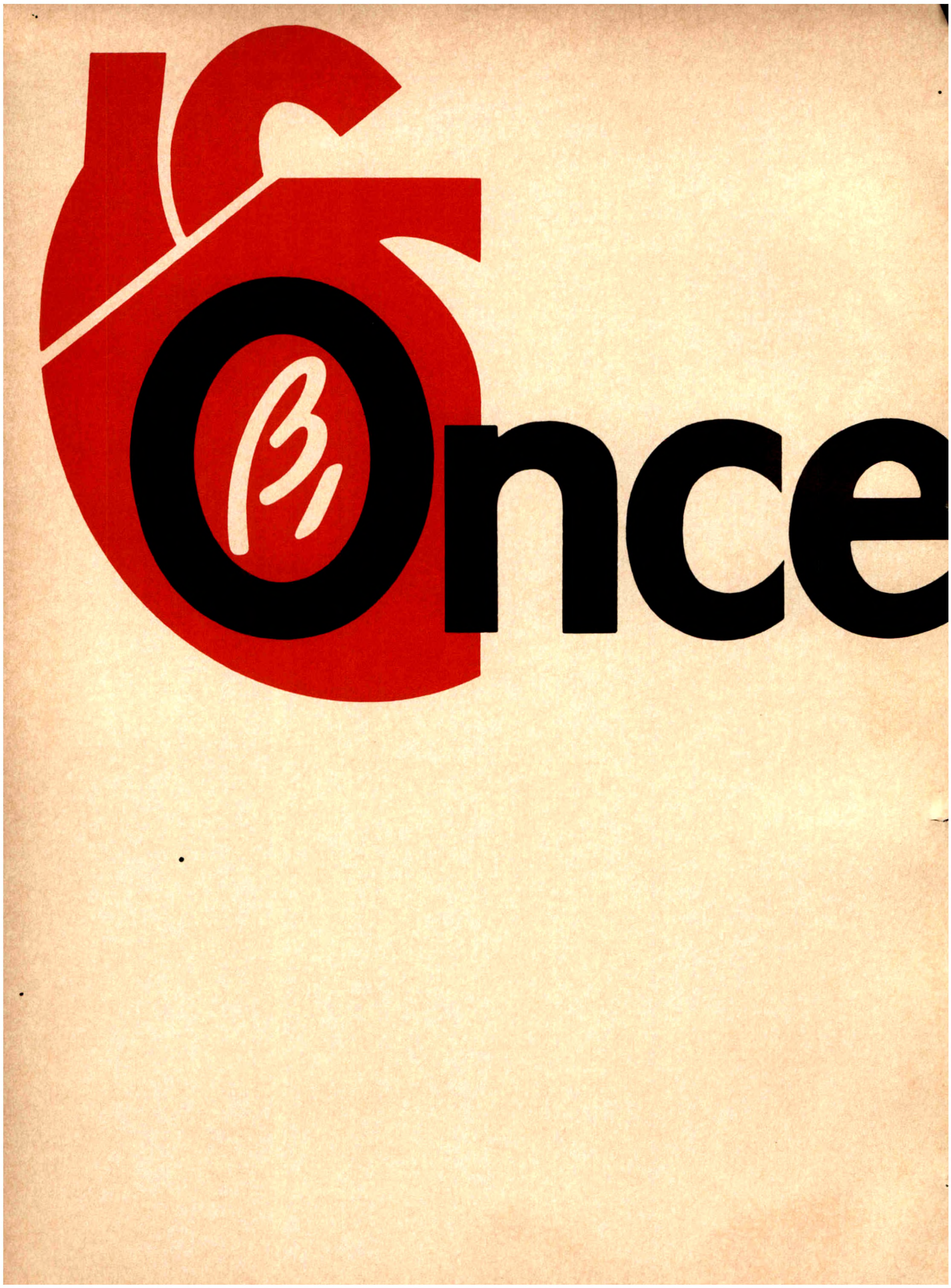
5. Advanced Cardiac Data Calculations

Dynex/C's comprehensive software and powerful computer enable precise measurements and on-line calculations of many vital cardiac parameters. Frozen M-mode displays give aortic and mitral valve stroke volume and flow, pre-ejection/ejection time ratio, fractional IVS shortening, and over 30 other values.

Left ventricular volume is determined from 2-D images using *six* advanced calculation methods. Stroke volume, cardiac output, ejection fraction, cardiac index and more, are computed and displayed.



Dynex C: we speak from a position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New dosage schedule: To start, 100 mg once-a-day, or in divided doses.

Lower doses (especially 100 mg) may not maintain full effect at end of 24-hour period. Measure BP near end of dosing interval, adjust to larger or more frequent dosage if needed.

*exerts a relative preference for beta-one receptors; this preference is not absolute.

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please turn page for brief Prescribing Information.

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Now more convenient than ever in once-a-day dosage

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References

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An antihypertensive beta-blocking agent

Tablets of 50 mg
Tablets of 100 mg

Prescribing Information

Brief Summary of Prescribing Information.

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

perthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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TR and was preserved in the other groups, including those with mild TR. The critical diameter was determined to be between the maximal diameter in the rheumatic patients without TR and the minimal diameter in the patients with moderate to severe TR, or 27 mm/m^2. Thus this easily measured variable can determine the presence and significance of functional TR, adding objectivity to the angiographic diagnosis of TR.

159 Effect of Pericardiocentesis on Right and Left Ventricular Function and Volumes in Pericardial Effusion

DANTE E. MANYARI, WILLIAM J. KOSTUK, and PAUL PURVES

Radionuclide techniques were used to measure right and left ventricular ejection fraction and volume changes produced by pericardiocentesis in patients with pericardial effusion. During 14 studies, mean right and left ventricular ejection fractions did not change significantly after removal of 527 ml (range 140 to 1,100) of pericardial fluid. Similar ejection fraction changes were observed in 4 subgroups: patients with and without cardiac tamponade and patients with normal and subnormal left ventricular function. End-diastolic and end-systolic volumes increased significantly after pericardiocentesis in both ventricles, but these changes were comparatively larger in the right ventricle. Volume changes were more marked in patients with than in those without cardiac tamponade. Thus, hemodynamic and clinical improvement after pericardiocentesis may be related only to an increase in stroke volume. The ejection fraction, a measure of myocardial contractility, remained unchanged.

163 Acute Effects of Phlebotomy on Right Ventricular Size and Performance in Polycythemic Patients With Chronic Obstructive Pulmonary Disease

ALLAN D. ERICKSON, WILLIAM A. GOLDEN, BEN C. CLAUNCH, WALTER E. DONAT, and JOHN T. KAEMMERLEN

Equilibrium radionuclide angiography was performed in 10 patients with severe chronic obstructive pulmonary disease and erythrocytosis before and immediately after phlebotomy. The mean right ventricular ejection fraction was abnormal before (0.38) but not after (0.43) phlebotomy and the increase was highly significant ($p < 0.001$). Similarly, the right ventricular end-diastolic area, a reflection of ventricular volume, decreased significantly, from 588 to 505 pixels ($p < 0.02$). No significant changes occurred on the left side; cardiac output was well maintained. If afterload was unchanged, as has been reported, these data are consistent with the hypothesis that a normalization in preload shifts the Starling curve, resulting in improved right ventricular performance with preservation of cardiac output.

167 Left Ventricular Performance During Exercise: Response of Ear Densitogram Derivative

BRUCE G. HAFFTY, TETSURO SUGIURA, NANCY E. O'HARE, and DAVID H. SPODICK

The peak ear densitogram derivative slowly increased throughout exercise in normal subjects to 2 minutes of recovery. In patients with coronary artery disease, the peak derivative rapidly increased to only 1 minute of exercise. Percent changes from control were significantly different, as were group differences at 1 minute ($p < 0.01$) and 4 minutes of exercise ($p < 0.05$) and 2 minutes after exercise ($p < 0.05$).

172 Effect of Cimetidine on the Pharmacokinetics and Pharmacodynamics of Quinidine

BRIAN G. HARDY, ISTVAN T. ZADOR, LAWRENCE GOLDEN, DAVID LALKA, and JEROME J. SCHENTAG

The influence of cimetidine on the disposition and pharmacodynamic effects of a single oral dose of quinidine was evaluated in 6 normal volunteers. After cimetidine pretreatment (1.2 g/day for 7 days), statistically significant increases in quinidine mean elimination half-life of 55% (range 30 to 109), peak plasma concentration of 21% (range 8 to 61), and time to peak concentration of 33% (range 8 to 118) were observed. An overall decrease in mean apparent oral clearance of 37% (range 23 to 49) resulted, without any significant changes in plasma protein binding or urinary excretion of unchanged drug. Cimetidine-induced changes in the pharmacokinetics of quinidine were accompanied by increases in simultaneously measured electrocardiographic effect variables. Changes in the Q-T interval, rate-corrected Q-T, QRS, and R-R intervals after a single dose of quinidine sulfate (400 mg) were significant. Treatment with cimetidine potentiated these pharmacodynamic responses, but failed to achieve significant differences from quinidine alone.

EXPERIMENTAL STUDIES

177 Relation Between Functional Response to Nitroglycerin and Extent of Myocardial Necrosis in Dogs: Mapping of the Left Ventricle by 2-Dimensional Echocardiography

KEICHO SHIMOURA, SAMUEL MEERBAUM, TATSUO SAKAMAKI, SHUJI KONDO, MICHAEL C. FISHBEIN, JACOB Y-RIT, CHUWA TEI, PRAVIN M. SHAH, and ELIOT CORDAY

Segmental 2-dimensional (2-D) echocardiographic study of left ventricular (LV) segmental response to discrete nitroglycerin infusion was performed in closed-chest dogs during acute occlusion of the left anterior descending

Continued on page A59

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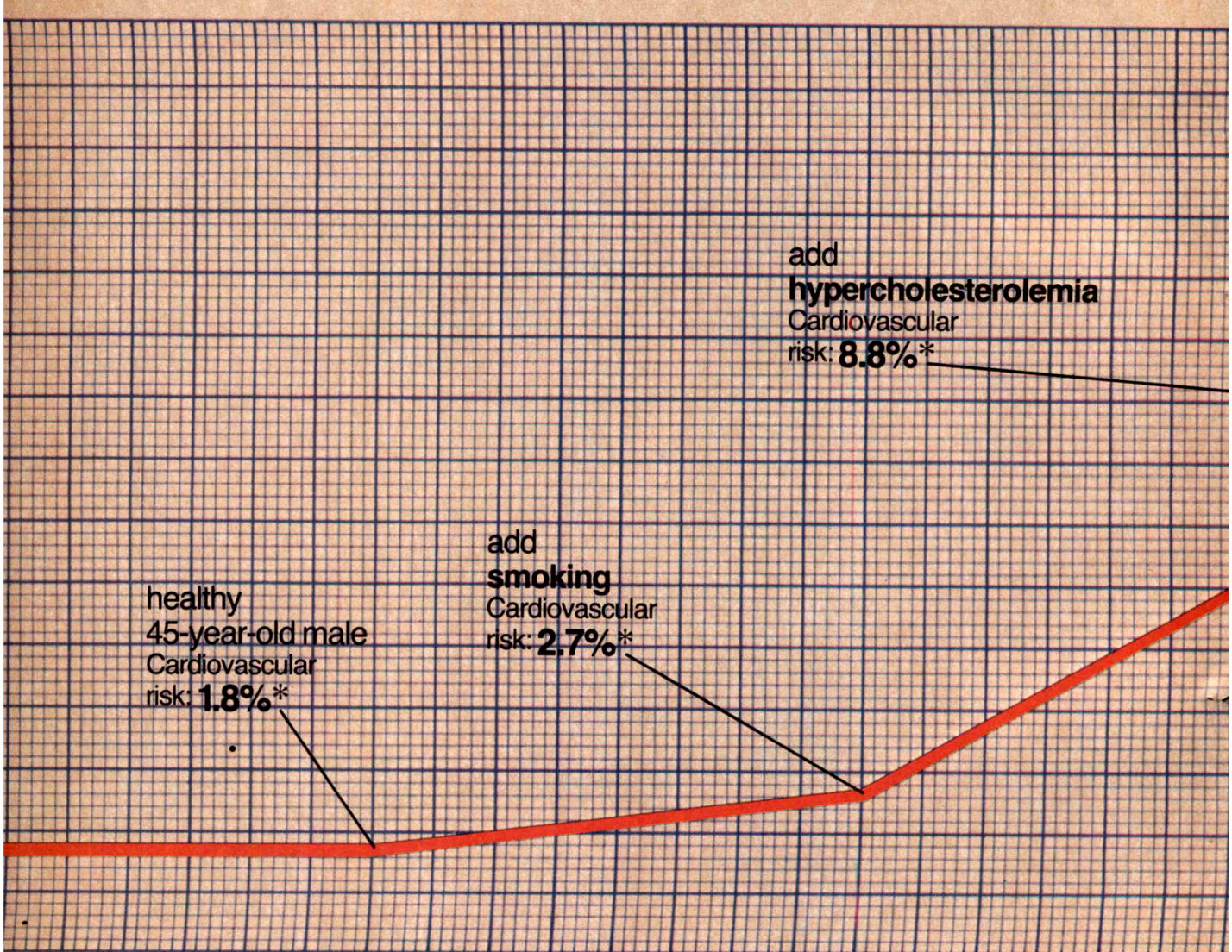

Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing

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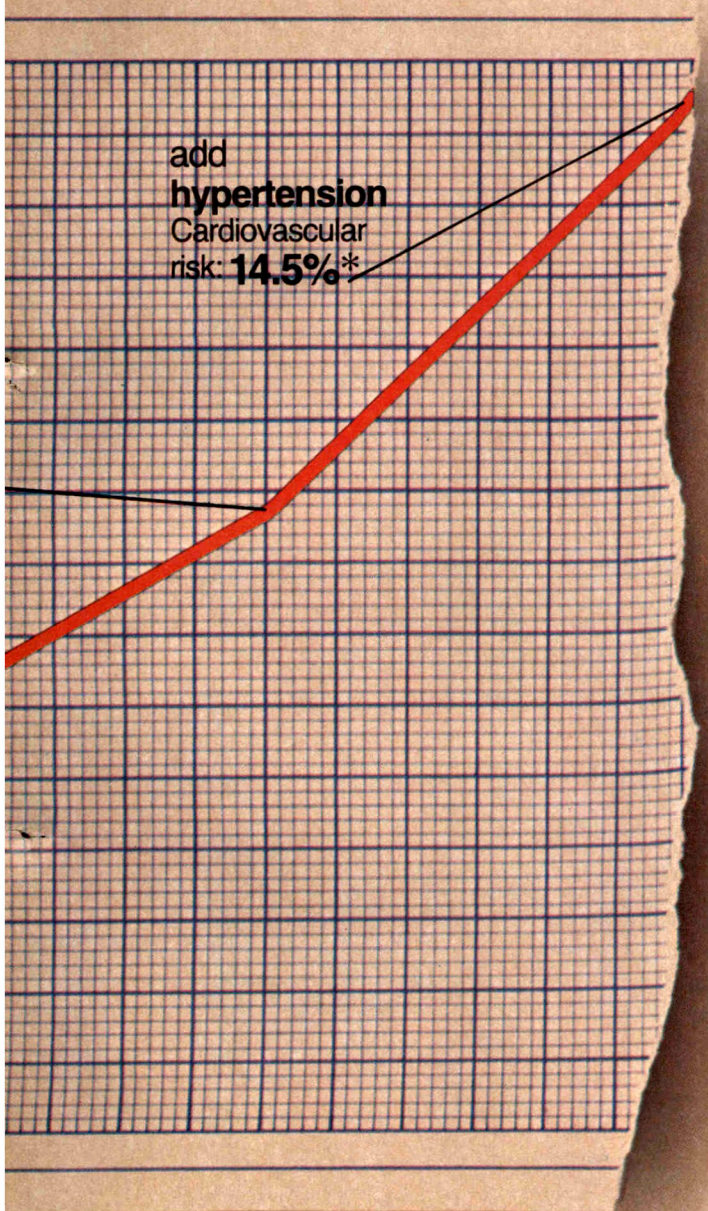

- When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

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†Minipress is not indicated for the treatment of hyperlipidemia.

Please see Minipress brief summary on following page.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

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Minipress® (prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

B.I.D. Dosage Convenience

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*
INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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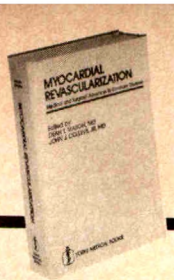

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coronary artery, and this response was related to the extent of necrosis found in equivalent segments of corresponding pathologic slabs. Remote nonnecrotic segments always responded to nitroglycerin by significant augmentation of segmental LV function (systolic fractional area change and systolic wall thickening). Five hours after occlusion, segments with necrosis <40% exhibited a significant nitroglycerin-induced potentiation in segmental LV function, whereas segments with necrosis >60% showed no potentiation with nitroglycerin. Segments with eventual necrosis >80% had no significant potentiation as early as 30 minutes after occlusion. It is concluded that nitroglycerin-induced potentiation of segmental LV function is closely associated with the extent of segmental myocardial necrosis and that 2-D echocardiographic study of potentiation might be useful for characterizing viability of ischemic myocardium.

184 Nuclear Magnetic Resonance Imaging of Acute Myocardial Infarction in Dogs: Alterations in Magnetic Relaxation Times

CHARLES B. HIGGINS, ROBERT HERFKENS, MARTIN J. LIPTON, RICHARD SIEVERS, PHILIP SHELDON, LEON KAUFMAN, and LAWRENCE E. CROOKS

Nuclear magnetic resonance imaging was used to study 24-hour-old acute myocardial infarctions in 8 excised canine hearts. Spin echo nuclear magnetic resonance imaging in each instance demonstrated the area of infarction as a region of increased signal intensity compared that in normal myocardium. For each dog the T1 value was greater for the infarct region; however, the group mean value for T1 of the infarct region was not significantly greater than that for the normal region. The T2 value was discriminate for all dogs, and the mean value for the infarct region was significantly different from that for normal myocardium.

189 Effects of Coronary Occlusion on Flow in the Distribution of a Neighboring Stenotic Coronary Artery in the Dog

JEFFREY S. SCHWARTZ, JAY N. COHN, and ROBERT J. BACHE

The effect of left anterior descending (LAD) coronary occlusion on flow through a stenotic left circumflex artery (LC) was studied in open-chest dogs. In the presence of a severe LC stenosis, LAD occlusion caused an increase in LC stenosis resistance and a decrease in blood flow through the stenotic LC. Partial collapse of the LC stenosis due to a decrease in intraluminal pressure in the stenotic segment may have been responsible for this finding. In a second group of dogs the LC stenosis was adjusted so that anterograde flow through the LC did not change after LAD occlusion. However, subendocardial flow (measured with radioactive microspheres) to the area supplied by the stenotic LC decreased, possibly because of a decrease in coronary pressure distal to the stenosis and an increase in left ventricular diastolic pressure. A decrease in flow to myocardium supplied by a stenotic coronary artery may occur when a neighboring artery is occluded.

196 Roles of the Right Ventricular Free Wall and Ventricular Septum in Right Ventricular Performance and Influence of the Parietal Pericardium During Right Ventricular Failure in Dogs

MASATO TANI

The roles of the right ventricular (RV) free wall and ventricular septum in RV performance were studied in the canine heart with the pericardium intact. Acute ischemia of the RV free wall decreased the RV stroke work index more than that of the ventricular septum. The response of the RV stroke work index to volume loading was also decreased. Combined RV free wall and ventricular septal ischemia produced more severe and predominant RV dysfunction. After combined ischemia, pericardiotomy improved the RV stroke work index as well as the left ventricular stroke work index, although the increase in the former was greater than that in the latter. The results of this study suggest that (1) the RV free wall was a more important role than the VS in RV performance, (2) predominant RV failure can be induced experimentally, and (3) the pericardium has a restrictive effect on the damaged and dilated right ventricle.

203 Effect of Fluocarbon Exchange Transfusion on Myocardial Infarction Size in Dogs

GRAHAM R. NUNN, GARLAND DANCE, JENNIFER PETERS, and LAWRENCE H. COHN

Fluosol DA (20%), a perfluocarbon with high oxygen solubility, was administered by concurrent exchange transfusion (30 ml/kg) to anesthetized, open-chest, adult greyhounds (n = 9) 1 hour after left anterior descending coronary ligation. Mechanical ventilation using 100% oxygen was used throughout. A second similar group (n = 9) received 0.9% normal saline solution (30 ml/kg) and a third group (n = 9) received no further intervention. Systemic, right atrial and left atrial pressures were not altered by the exchange transfusion. Vital stain dye techniques were used to define areas at risk (A_R) (monastryl blue) and necrosis (A_N) (triphenyltetrazolium chloride). Fluosol DA significantly decreased the A_N/A_R ratio compared with values in the control and saline solution groups. Thus, fluocarbon exchange transfusion may reduce infarct size when administered after coronary occlusion.

Continued on page A63

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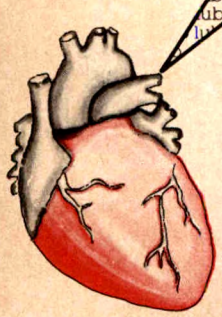

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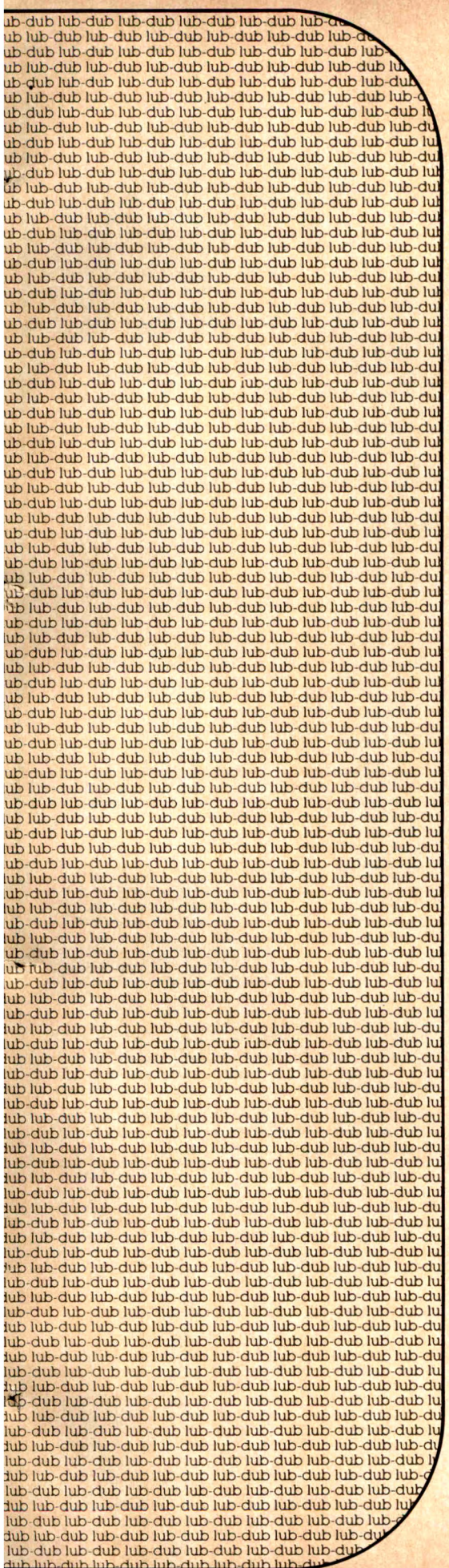

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Acute psychosis, cholestatic ndice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory culty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be in-dualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day n in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete scribing information for dosage recommendations.**

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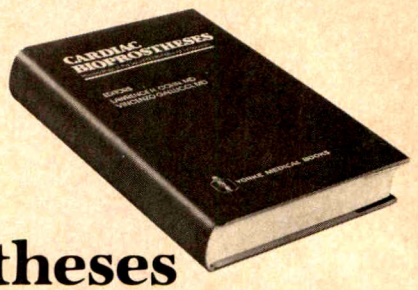

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

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Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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VOLUME 52

NUMBER 1

CORONARY HEART DISEASE

Intracoronary Thrombus in Nontransmural Myocardial Infarction and in Unstable Angina Pectoris

JAY B. MANDELKORN, MD, NELSON M. WOLF, MD, SURENDER SINGH, MD, JAY A. SHECHTER, MD, ROBERT I. KERSH, MD, DAVID M. RODGERS, MD, MARK B. WORKMAN, MD, LAMBERTO G. BENTIVOGLIO, MD, STEVEN M. LaPORTE, MD, and STEVEN G. MEISTER, MD,
With the technical assistance of BARBARA TUCKER

Although intracoronary thrombus formation plays a major role in acute transmural myocardial infarction (MI), its occurrence in unstable angina (UA) and nontransmural MI has not clearly been established. To determine whether intracoronary thrombus does occur in these syndromes, coronary arteriography was performed before, during, and after intracoronary nitroglycerin and streptokinase infusion in 17 patients. None of the 8 patients with nontransmural MI and 1 of the 9 patients with UA responded to intracoronary nitroglycerin. Seven of 8 patients with nontransmural MI and 4 of 9 patients with UA responded to streptokinase infusion with opening of an occluded vessel, an increase in stenotic diameter, dissolution of an intracoronary filling defect, or a combination of these. Serial opening and closing of ischemia-related vessels occurred spontaneously and in response to streptokinase in some patients in whom thrombolysis was demonstrated. Evidence of thrombolysis was not seen in any patient studied longer than 1 week from the onset of the rest pain syndrome.

The finding of thrombolysis in several patients with nontransmural MI and UA suggests that intracoronary thrombus formation plays a pathogenetic role in some patients with these ischemic syndromes.

Recent necropsy[1–3] and angiographic studies[4–7] have established that intracoronary thrombus plays an important role in the genesis of acute transmural myocardial infarction (MI). However, evidence of thrombus involvement in the pathogenesis of nontransmural MI and unstable angina (UA) is less clear. Roberts and Buja[8] found no intracoronary thrombus at necropsy in 8 patients dying after nontransmural MI. Similarly, Erlich and Shinohara[9] found intracoronary thrombus in only 2 of 20 such patients at autopsy. Rentrop et al[6] found no angiographic evidence of clot lysis when 5 patients with UA were given intracoronary streptokinase. However, Vetrovec et al[10] and Holmes et al[11] both described intracoronary lucencies suggestive of intracoronary thrombi as an infrequent finding in some patients undergoing cardiac catheterization for UA or nontransmural MI. However, these intracoronary lucencies were not positively identified as thrombus in either study. To further clarify whether intracoronary thrombus does occur in these syndromes, we performed coronary arteriography before, during, and after in-

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TABLE I Nontransmural Myocardial Infarction

Patient	Age (yr) & Sex	Time Since Instability (days)	Longest Duration of Rest Pain (min)	ECG	Creatine Kinase (normal <110 IU liter) Before Study	Creatine Kinase (normal <110 IU liter) After Study	Ischemia-Related Vessel	% Stenosis Before Streptokinase	% Stenosis After Streptokinase	% Stenosis Delayed Study	Defect Index (DI) Before S/K	Defect Index (DI) After S/K	Defect Index (DI) Delayed Study
FE	54M	5	<15	Old Inferior MI ST↓ laterally	189	1,425	LC	80	38	40	1.3	0.2	0
RK*	63M	2	45	T↓ inferior	58	165	Right	86	25	30	1.3	0.6	0
MA	56F	9	120	S-T↓ lateral	172	147	LC	78	62	. . .	0	0	. . .
JY†	59M	6	60	Old inferior MI S-T↑ anterior	193	442	Right	67	62	Occluded	2.1	1.1	Occluded
EG‡	51M	1	120	T↓ lateral	189	483	LC	83	71	55	1.6	0.6	0
SC*	66F	1	30	Nonspecific T flattening	231	38	LC	92	67	. . .	0.7	0	. . .
RJ	52M	5	30	T↓ inferior	133	33	Right	84	84	82	0.4	0	0
AC‡	55M	5	40	T↓ anterior ST↑ with pain	49	304	LAD	84	85	84	0.8	0	0

* Initially stenosed vessel became occluded during study and reopened with streptokinase.
† Both LAD and circumflex occluded; RCA gave collaterals to both systems (see text).
‡ Initially occluded vessel reopened with angiographic dye only (to 83%).
DI = Defect index = ratio of any consistent diameter of the filling defect to adjacent vessel diameter (see methods); ECG = electrocardiogram; LC = left circumflex; LAD = left anterior descending; MI = myocardial infarction; RCA = right coronary artery.

TABLE II Unstable Angina

Patient	Age (yr) & Sex	Time Since Instability (days)	Longest Duration of Rest Pain (min)	ECG	Creatine Kinase (normal <110 IU/liter) Before Study	Creatine Kinase (normal <110 IU/liter) After Study	Ischemia-Related Vessel	% Stenosis Before Streptokinase	% Stenosis After Streptokinase	% Stenosis Delayed Study	Defect Index (DI) Before S/K	Defect Index (DI) After S/K	Defect Index (DI) Delayed Study
JH	61M	6	60	WNL	72	. . .	Right	80	45	50	0.9	0.7	0
JM*	54M	7	90	ST↑ inferior with pain	56	49	Right	79	79	54	0.6	0	0
WO	37M	6	180	T↓ inferior	53	31	Right	83	83	82	0.4	0	0
GB	63M	21	<15	T↓ inferior	36	60	Right	92	83	86	0	0	0
HB	66F	20	20	T↓ anterior	74	65	LAD	88	88	. . .	0	0	. . .
RG	66M	40	20	Diffuse ST-T	86	105	LC	89	80	. . .	0	0	. . .
CL†	63M	1	<15	T↓ anterior	110	86	LAD	92	70	90	0.5	0.4	0.4
EM	59F	60	60	WNL	56	45	LC	69	67	. . .	0	0	. . .
RR	44F	30	45	T↓ anterior	31	32	LAD	80	83	. . .	0	0	. . .

* Initially occluded vessel reopened with NTG 200 μg intracoronary (see text).
† Initially occluded vessel reopened with angiographic dye only (see text).
WNL = within normal limits; other abbreviations as in Table I.

tracoronary streptokinase infusions in 17 patients with recent severe UA or nontransmural MI.

Methods

The patients in this study were drawn from the general population of patients referred for cardiac catheterization at our institution between March 1981 and February 1982. Group I consisted of 8 patients with nontransmural MI. These patients had either prolonged or frequently recurrent pain at rest. All had abnormal electrocardiograms, but none evolved pathologic Q waves. All patients had an increase in total creatine kinase to >150% of laboratory normal within 24 hours of their ischemic symptoms. Creatine kinase, myocardial band, was detected in all of these patients. Clinical features in Group I patients are summarized in Table I.

Group II consisted of 9 patients with severe UA or intermediate syndrome. The clinical and electrocardiographic profile was similar to that of the Group I patients. However, none of these patients had elevation of creatine kinase or its myocardial fraction. Clinical features of Group II patients are summarized in Table II.

Patients with bleeding diatheses, hemorrhagic peptic ulcer disease, recent cerebrovascular accident, recent surgical procedures, prior exposure to streptokinase, or age >70 years were excluded from the study. Only patients with a readily identifiable ischemia-related vessel were included in the study. We defined an ischemia-related artery as that occluded or stenosed vessel most closely corresponding to an electrocardiographically or ventriculographically determined area of ischemia, or an isolated coronary artery stenosis >70%. Only a small fraction of patients with UA and nontransmural MI fulfilled these criteria, gave informed consent, and were included in this study.

Left ventriculography and selective coronary arteriography using the Judkins technique were performed. After initial visualization of the coronary anatomy, a bolus of 200 μg of nitroglycerin was given directly into the ischemia-related vessel and angiography was repeated. Streptokinase was then infused directly into the ischemia-related artery at 4,000 units/min for the first 60 minutes and at 2,000 units/min for the next 30 minutes. Repeat coronary arteriograms were performed at 15 minutes intervals during streptokinase infusion in the projection best demonstrating the obstructing lesion. Creatine kinase and its myocardial fraction were obtained immediately before and after streptokinase infusion and at 6-hour intervals for 48 hours thereafter.

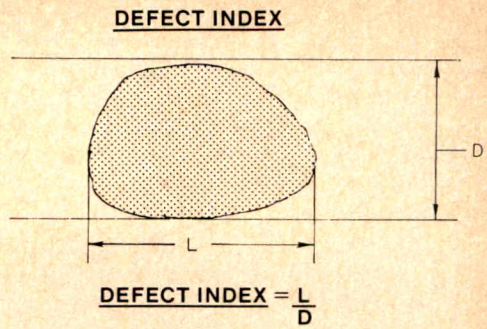

FIGURE 1. Scheme for determination of the defect index. D = any consistent adjacent diameter of the vessel; L = any consistent diameter of the filling defect.

All measurements of coronary anatomy were made by at least 2 independent observers from the screen of a model XR-35 Vanguard projector. A magnifying glass calibrated in 0.5 mm gradations was used. To determine the percentage of stenosis, the narrowest stenotic diameter was compared with the diameter of an uninvolved segment located immediately distal in the vessel. Measurements on single frames, in identical projections, were made before and after nitroglycerin, at the conclusion of streptokinase infusion, and at the time of the delayed study if this was performed.

A positive anatomic response to nitroglycerin or streptokinase was defined as conversion of an occluded vessel to a patent vessel, a change in stenosis diameter >20% in any consistent projection,[12] or dissolution of or a measurable decrease in the size of an intraluminal filling defect. To quantitate changes in the size of filling defects, we devised a defect index (Fig. 1). This index related any consistent diameter of the filling defect to the diameter of the vessel measured nearby in order to cancel out magnification effects. In a series of 20 separate measurements we found that interobserver variance in calculating this index did not exceed 20%. Accordingly, a 40% or greater reduction in the defect index was considered to be measurable and to represent thrombus lysis.

Ten patients (6 in group I and 4 in group II), responding to streptokinase, had repeat angiography 7 to 14 days after initial study. All were maintained on anticoagulation with intravenous heparin in the interim.

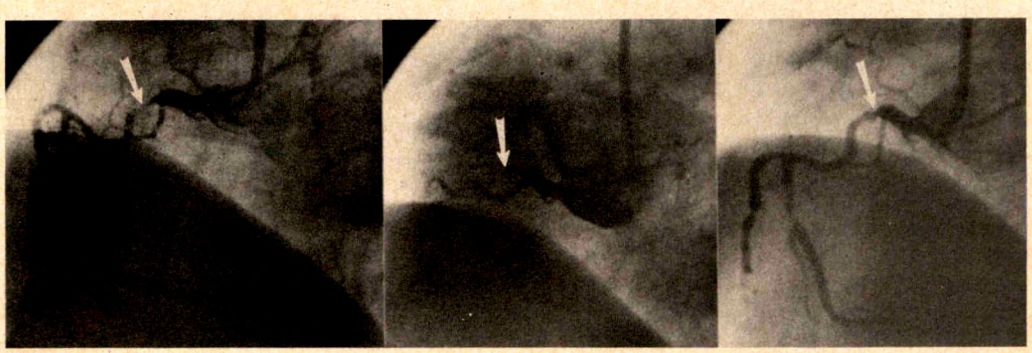

FIGURE 2. Right coronary artery in the left anterior oblique projection in patient RK with nontransmural myocardial infarction and recurrent chest pain episodes (see text). **Left panel,** the initial appearance of the right coronary artery. The **arrow** points to a translucent intraluminal filling defect giving the appearance of severe stenosis. **Middle panel,** the same vessel during an episode of chest pain. The vessel is occluded at the site of the filling defect (**arrow**). The vessel failed to reopen with intracoronary nitroglycerin. **Right panel,** the same vessel after streptokinase infusion. The vessel is now reopened and the stenosis has been markedly reduced. Nearly complete dissolution of the filling defect has occurred. The **arrow** points to the area where the filling defect was previously seen.

Results

Group I: nontransmural MI: Seven of 8 patients with nontransmural MI had anatomic changes in response to streptokinase infusion and were considered to have had lysis of intracoronary thrombi. No patient had any change in response to intracoronary nitroglycerin. All 7 responding patients had reduction of their filling defect indexes >40%. In 3 the defect was no longer visible at the conclusion of streptokinase infusion. Four patients also had a significant increase in luminal diameter at the site of stenosis. Two of these patients (EG and AC in Table I) had totally occluded ischemia-related vessels on initial angiography. In both, the vessels were unaffected by intracoronary nitroglycerin. Both partially reopened spontaneously and subsequently showed significant reduction or total elimination of the filling defect in response to streptokinase. Two other patients (RK and SC in Table I) had initially patent ischemia-related vessels which became totally occluded during the course of the study. Neither responded to intracoronary nitroglycerin but both reopened during streptokinase infusion and ultimately showed substantial improvement over their original anatomy at the end of the infusion (Fig. 2).

Six of the 7 patients in Group I initially responding to streptokinase were anticoagulated with intravenous heparin infusions sufficiently long to prolong partial thromboplastin 2 to 3 times normal and restudied within 2 weeks. In 3 patients who had residual filling defects, these were found to have undergone complete dissolution. One of these patients also showed subsequent improvement of stenotic diameter. Two other patients showed no change from their immediate poststudy status. One patient was restudied on an emergency basis because of total occlusion of the ischemia-related vessel, when heparin was discontinued in preparation for surgery (Fig. 3).

Group II: unstable angina: Four of 9 patients in this group had a positive anatomic response to streptokinase, 2 with an increase in stenotic diameter and 2 with complete dissolution of a filling defect. One of these (JM in Table II) initially reopened a totally occluded vessel in response to intracoronary nitroglycerin, leaving a major stenosis and an intraluminal defect that was then

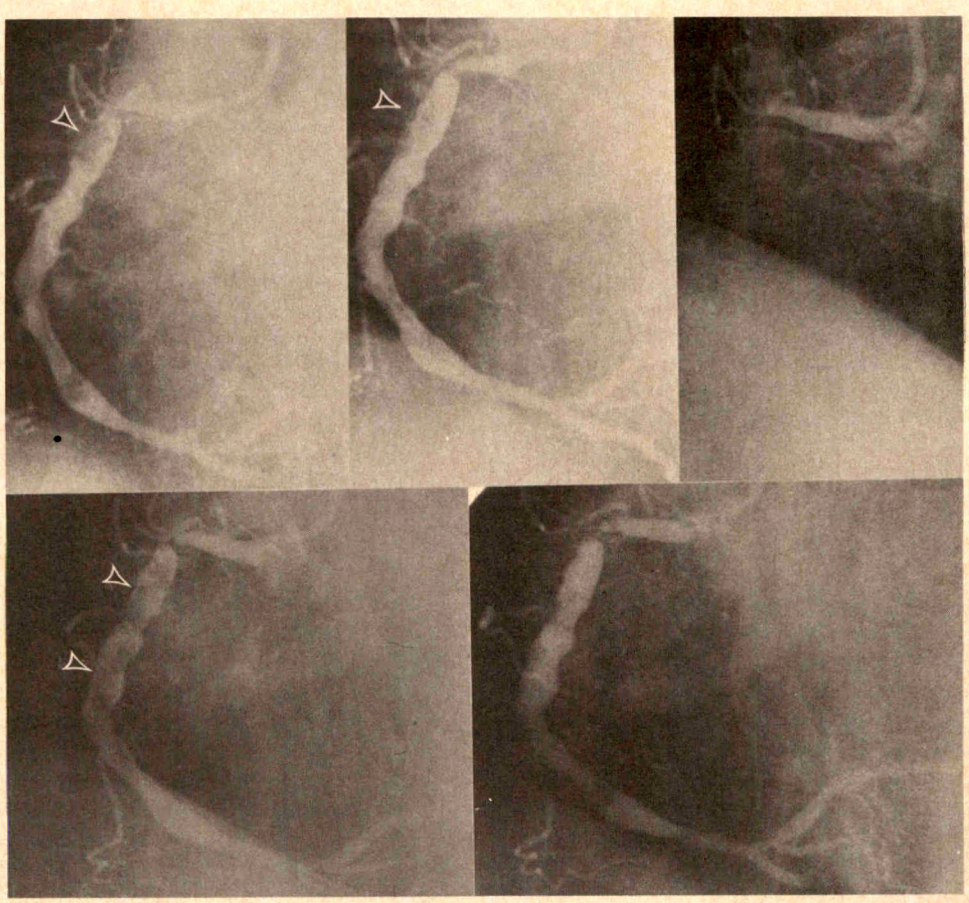

FIGURE 3. Right coronary artery in the left anterior oblique projection from patient JY with an acute nontransmural myocardial infarction (see text). **Top left panel,** the initial appearance of the right coronary artery. Severe proximal stenosis is associated with a large filling defect (**arrow**). **Top middle panel,** the vessel after streptokinase infusion. The stenosis is unchanged. The filling defect has decreased in size and is barely visible (**arrow**). **Top right panel,** a study performed 10 days after streptokinase infusion. Two hours after heparin was stopped, the patient had recurrent chest pain. The right coronary artery is occluded at the site of the previous stenosis. Intracoronary nitroglycerin failed to reopen the vessel. **Bottom left panel,** the vessel after reopening with intracoronary urokinase. Large filling defects are seen (**arrows**). Later in the infusion these defects embolized distally. **Bottom right panel,** taken after completion of urokinase infusion. The filling defects are no longer seen.

eliminated by streptokinase. Another patient (CL in Table II) initially reopened a totally occluded vessel in response to angiographic dye alone, leaving severe stenosis and an apparent filling defect. Intracoronary nitroglycerin produced no further change. Streptokinase infusion increased the vessel diameter at the stenotic site. An example of a patient from Group II is seen in Figure 4.

Two patients initially responding to streptokinase showed further anatomic change on restudy after 1 week of anticoagulation with heparin. One had a significant increase in luminal diameter. The other showed complete disappearance of a large intraluminal filling defect.

Although most patients were studied the day of the chest pain episode, we were unable to demonstrate thrombolysis in any patient in either group who was studied longer than 1 week after the onset of the rest pain syndrome.

Discussion

We found evidence of angiographic changes in the ischemia-related vessels when streptokinase was administered to 7 of 8 patients with nontransmural MI and 4 of 9 patients with UA. In all instances, the changes reported were visible to the unaided eye. Measurements were made to provide quantitative documentation. These findings establish the occurrence of intracoronary thrombus in some patients with these 2 syndromes. As such, they are in keeping with several earlier observations implicating thrombus formation in the pathogenesis of these syndromes. Folts et al[13] demonstrated spontaneous intermittent occlusions of partially obstructed canine coronary arteries by platelet thrombi. Hirsh et al[14] showed increased transmyocardial thromboxane B_2 ratios in patients with UA, whereas Sobel et al[15] demonstrated increased circulating levels of platelet specific factors (beta thromboglobulin and platelet factor IV) shortly after episodes in man. Neill et al[16] observed a high incidence of total occlusion of previously patent ischemia-related vessels in patients restudied 4 months after episodes of UA. Interestingly, Lawrence et al[17] performed a small prospective controlled study of intravenous fibrinolytic therapy in patients with unstable angina pectoris. In a 6-month follow-up, they found significantly fewer cardiovascular events in the streptokinase-treated patients than in the controls. Vetrovec et al[18] administered streptokinase to 7 patients with unstable ischemic syndromes related to obstructions in the native coronary vessels. Minor angiographic changes were noted in 4 and major changes only in 1 patient. Because in that individual a guide wire was employed to reopen the vessel, thrombolysis was not clearly established.

The absence of evidence for intracoronary thrombus in 5 of 9 of our patients with UA and 1 of 8 patients with nontransmural MI suggests that other processes such as coronary spasm may have been involved. In this connection, Parodi et al,[19] using scintigraphic techniques, demonstrated episodic reduction in regional myocardial perfusion in patients with UA during rest pain. These investigators attributed this finding to intermittent coronary artery spasm. Moreover, Maseri et al[20] observed coronary spasm angiographically in some "preinfarctional" patients.

Alternatively, our methods may not have been sufficiently sensitive to detect intracoronary thrombus in all patients in whom it may have occurred. In experimental preparations of Folt et al[13] intracoronary thrombi formed, disappeared, and reformed respectively over a period of minutes of hours, causing intermittent vessel obstruction in the process. It is conceivable that a similar process occurs during UA in man and that intracoronary thrombi are not always present or sufficiently large and distinct enough to be visualized at the time of angiography. We did not document intracoronary thrombus in any patient who was studied longer than 1 week after the onset of unstable symp-

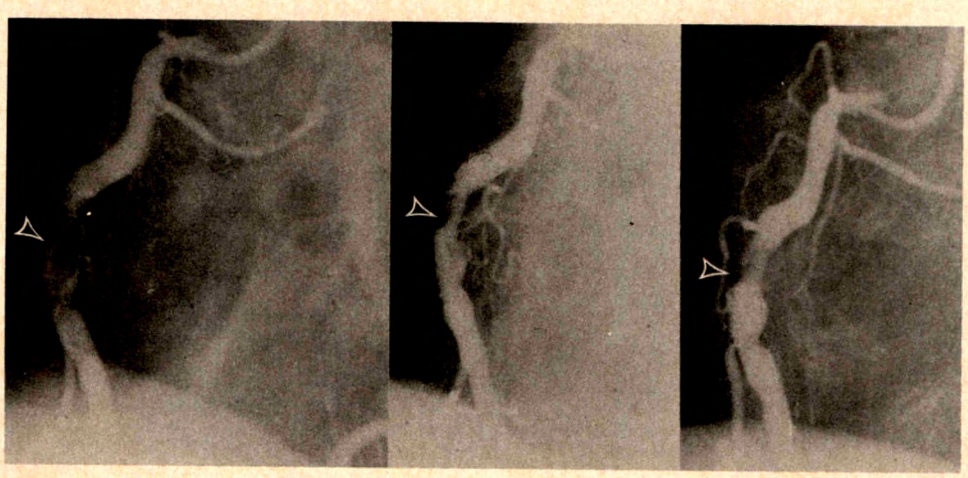

FIGURE 4. Right coronary artery in the left anterior oblique projection from patient JH with unstable angina (see text). **Left panel,** the initial appearance of the right coronary artery. There is a severe stenosis of the proximal vessel associated with a globular intraluminal filling defect (**arrow**). **Middle panel,** taken immediately after streptokinase infusion. The stenosis (**arrow**) was reduced significantly, but the filling defect has not been measurably decreased. **Right panel,** after 6 days of heparin therapy. The severity of the stenosis is unchanged (**arrow**) and the filling defect is no longer present.

toms. Moreover, intracoronary thrombi that may have been present for some time became organized and no longer subject to lysis by streptokinase.

Our experience does suggest an alternative mechanism for episodic reduction in regional myocardial perfusion, namely, intermittent obstruction of a coronary artery by thrombus superimposed on preexisting atherosclerotic obstructive lesions. We observed this process angiographically at various stages in one of our patients with unstable angina (CL) and in 4 patients with nontransmural myocardial infarction (RK, JY, SC, AC).

These observations also suggest a possible common cause of severe unstable angina pectoris: nontransmural and transmural myocardial infarction. Intracoronary thrombus formation may be a common factor in all 3. The specific clinical syndrome that results may be a function of the duration of total obstruction as well as the size and extent of the coronary artery or branch involved and the availability of collateral circulation. It must be emphasized that the patients included in this study represented only a fraction of the patients with unstable angina or nontransmural myocardial infarction seen in our institution during the study. Thus, no inferences regarding the true incidence of intracoronary thrombus in these conditions can be drawn. Obviously, further study is needed to delineate the incidence and importance of intracoronary thrombus in these ischemic syndromes as well as to critically explore the possible therapeutic potential of pharmacologic agents capable of lysing or preventing intracoronary thrombi.

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Comparison of High-Dose and Medium-Dose Propranolol in The Relief of Exercise-Induced Myocardial Ischemia

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The effects of medium-dose (160 mg/day) and high-dose (480 mg/day) oral propranolol were compared in 22 patients who had typical angina pectoris and objective evidence of myocardial ischemia during exercise. Left ventricular (LV) ejection fraction (EF) and wall motion score (WMS) (an index of regional LV dysfunction) were assessed by radionuclide angiography both at rest and during exercise to the pretreatment maximum work load. Functional class improved in 11 of the 22 patients during medium-dose propranolol therapy. Medium-dose propranolol reduced mean resting heart rate from 71 to 55 beats/min, exercise heart rate from 122 to 93 beats/min, and exercise systolic blood pressure from 183 to 162 mm Hg ($p < 0.001$ for each). The incidences of exercise-induced chest pain and S-T segment depression were reduced from 19 to 9 patients ($p < 0.001$), and from 20 to 10 patients ($p = 0.002$), respectively. Medium-dose propranolol had no effect on mean EF or WMS at rest, but improved function in ischemic regions during exercise; WMS decreased ($p = 0.001$), and mean exercise EF increased from 0.51 to 0.56 ($p = 0.025$). Compared with the medium dose, high-dose propranolol improved functional class in 3 additional patients, and further reduced mean resting heart rate (from 55 to 52 beats/min, $p = 0.001$) and mean exercise heart rate (from 93 to 86 beats/min, $p = 0.001$). Exercise-induced chest pain and S-T segment depression were abolished in a further 7 and 6 patients, respectively. Exercise EF and WMS improved further in several patients, but the changes were not statistically significant for the group ($p = 0.095$ and 0.082, respectively).

Thus, in patients with coronary artery disease and exercise-induced ischemia, propranolol reduced heart rate and blood pressure and the incidence of exercise-induced chest pain, electrocardiographic changes, and ischemic LV dysfunction. Although most of these effects were seen with medium-dose propranolol, higher doses provided additional relief of chest pain and S-T segment depression, and further improved global and regional LV function in several patients.

Propranolol, a nonselective beta-adrenergic antagonist, has been used for many years in the management of patients with ischemic heart disease. Several studies have shown that propranolol decreases the heart rate and blood pressure responses to exercise, and is effective in reducing the frequency of anginal attacks.[1–5]

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Although it has been established that near-maximal beta-blockade is achieved with moderate doses of propranolol,[6] studies examining the effects of high doses of propranolol on symptoms, exercise tolerance, and left ventricular (LV) function in patients with ischemic heart disease have not yielded consistent results. Certain investigators have observed greater improvement in symptoms with high-dose than with medium-dose propranolol,[3,4] while others have noted that high-dose propranolol not only provided little additional benefit but also significantly impaired LV function.[7,8]

Several groups of investigators have reported recently[9,11] that propranolol in fixed daily doses ranging from 80 to 320 mg improved global and regional LV function during exercise in patients with coronary artery disease and exercise-induced myocardial ischemia; the relative effects of different doses were not compared in

these studies. The purpose of the present study was to compare the effects of medium-dose (160 mg/day) and high-dose (480 mg/day) propranolol on clinical symptoms and LV function in patients with typical angina pectoris and exercise-induced myocardial ischemia. Radionuclide measurements of global and regional LV function were compared at rest and at identical exercise work loads before and during treatment with medium-dose and high-dose propranolol. Plasma propranolol levels were measured to ensure drug compliance and to examine the relationship between plasma levels and measured effects of the drug.

Methods

Patient population: Twenty-two men aged 48 to 64 years participated in the study. All had typical angina pectoris, and had had angina and ≥1 mm horizontal or downsloping S-T segment depression during routine treadmill testing. Patients were required to have failure of the ejection fraction (EF) to increase by 0.05 and the appearance of a new wall motion abnormality during exercise radionuclide angiography.

Cardiac catheterization was performed for routine clinical indications in 12 patients. Significant coronary artery disease (defined by a ≥75% diameter stenosis of ≥1 major artery) was confirmed in each case; 5 patients had 2-vessel disease and 7 patients had 3-vessel disease. Myocardial infarction had been documented at least 3 months previously in 4 of the 12 patients who had undergone cardiac catheterization and in 7 of the 10 patients who had not. Ten patients were taking propranolol (40 to 160 mg/day) before entry into the study; the response to this therapy did not influence selection. No patient had symptoms of congestive heart failure.

Study protocol: Since this study concerned comparison of the effects of medium-dose and high-dose propranolol on objective indexes of LV function at equal work loads, an open protocol was used. The study involved 3 evaluations. Patients were first evaluated before commencement of the study drug; previously administered propranolol was discontinued for at least 2 weeks. The second evaluation followed 2 weeks of continuous therapy with 160 mg/day of propranolol. The dose was then increased to 480 mg/day and a third evaluation was performed 2 weeks later. In each case propranolol was given in 4 divided doses each day.

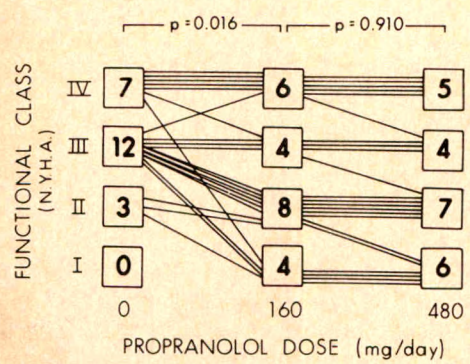

FIGURE 1. Clinical status, expressed as New York Heart Association (NYHA) functional class, of 22 patients with ischemic heart disease assessed before treatment with propranolol (0 mg/day) and subsequently during medium-dose (160 mg/day) and high-dose (480 mg/day) therapy. The number of patients in each functional class are shown for each of the 3 assessments. Probability (p) values were derived from chi-square analysis.

At each evaluation, a cardiovascular history was taken, a physical examination was performed, and a New York Heart Association functional class was assigned. Radionuclide angiography was performed at rest and during exercise.

Exercise radionuclide angiography: Each exercise test was performed with the patient in the postabsorptive state. All nitrates were withheld for at least 6 hours. For evaluations on the 2 doses of propranolol, tests were performed 2 to 3 hours after the previous dose; studies were scheduled for each patient at a similar time during the day. Patients exercised in the upright position on an isokinetic bicycle ergometer (Fitron, Lumex). The electrocardiogram was monitored continuously, and the standard limb leads and leads V_5 and V_6 were recorded initially and after each minute of exercise. Arterial blood pressure was measured by cuff manometry at rest and during each minute of exercise. Exercise began at 150 kpm/min (50 W); the work load was increased by 150 kpm every 3 minutes, at a constant pedalling rate of 60 rpm. For the pretreatment evaluation, exercise was continued until limited by moderate angina, ≥1 mm S-T segment depression, or severe fatigue. Each subsequent study was performed to the maximum level of work load achieved in the initial evaluation. To assess the effects of high-dose propranolol on exercise performance, patients were then encouraged to exercise further if they had not achieved 1 of the endpoints described above.

Multigated radionuclide angiograms were recorded by labelling red blood cells in vivo with 30 mCi of technetium-99m. Radionuclide angiograms were acquired using a Searle L.E.M. mobile scintillation camera with a high-sensitivity slant hole collimator, and an R-wave triggered gate interfaced to a Medical Data Systems A^2 computer. Studies were acquired in a histogram mode, in a 64 × 64 matrix of 24 frames each containing 125,000 counts. Acquisition time was approximately 1.5 to 2 minutes for each study; radionuclide angiograms were recorded before exercise and during the second and third minutes of the final exercise stage. Left ventricular EF was calculated using a varying region of interest technique. Regions were assigned by an operator-assisted semi-automated edge-detection program using standard software. Analysis of counts in each region allowed the construction of time-activity curves. Background-corrected end-diastolic (ED) and end-systolic (ES) counts were determined from the peak and trough of the time-activity curve respectively, and EF was calculated from the formula: EF = (ED counts − ES counts)/ED counts. LV wall motion was evaluated from an endless loop display of data from all 24 frames of the radionuclide angiogram. Wall motion was assessed by at least 2 blinded observers who arrived at a reading by consensus. The left ventriculogram in the left anterior oblique view was divided into 6 segments (2 septal, 2 inferoapical, and 2 posterolateral). A semiquantitative wall motion score (WMS) was calculated based on a score for each segment of normal = 0, hypokinetic = 1, akinetic = 2, and dyskinetic = 3.

Reproducibility of measurements: The reproducibility of the radionuclide measurements at rest and during maximal exercise was assessed in 9 men who had all criteria for the present study. Each patient underwent exercise radionuclide angiography on 2 occasions 1 to 2 weeks apart, without propranolol therapy. Initial exercise was performed to the endpoints previously described, and the second study was performed to an identical work load. The reproducibility of exercise-induced chest pain and S-T segment depression was also noted.

Serum propranolol levels: Blood samples were drawn 2 to 3 hours after propranolol administration. The plasma was removed after centrifugation and immediately refrigerated for subsequent measurement of propranolol levels. Serum

TABLE I Exercise Responses During Medium-Dose (P 160 mg) and High-Dose (P 480 mg) Propranolol Therapy

	Chest Pain			S-T Depression		
	+	−		+	−	
Pre	19	3	p = 0.002	20	2	p = 0.002
P 160 mg	9	13		10	12	
			p = 0.014			p = 0.049
P 480 mg	2	20		4	18	

Pre = pretreatment.

propranolol levels were measured by high-pressure liquid chromatography, using a modification of the technique described by Nation et al.[12]

Analysis: Functional improvement during therapy with medium-dose and high-dose propranolol therapy was assessed by chi-square analysis of the distribution of New York Heart Association functional class. Chi-square analysis was used also to compare the incidence of chest pain and S-T segment depression during exercise tests.

The nonparametric Wilcoxon signed-rank test for paired observations was used to assess differences (1) between pretreatment and medium-dose propranolol, and (2) between medium-dose and high-dose propranolol. Since assessment of more than 1 set of paired observations increases the chance of a "false significant" finding by approximately the number of sets tested,[13] a p value <0.03 was selected to indicate a significant change.

Results

Clinical responses: Clinical responses to different doses of propranolol are shown in Figure 1. Of the 22 patients studied, 11 improved by at least 1 functional class during therapy with medium-dose (160 mg/day) propranolol; however, 1 patient deteriorated from functional class III to functional class IV. During therapy with high-dose propranolol (480 mg/day), the patient who deteriorated to class IV during medium-dose therapy improved to class III; 2 patients who had not initially responded and 1 who had improved with medium-dose therapy improved by 1 functional class with the higher dose. Analysis of the group response showed significant overall improvement with medium-dose propranolol (p = 0.016) but no further change with high-dose therapy.

Exercise endpoints: Each of the 9 subjects who performed duplicate exercise tests without taking propranolol achieved the same maximum work load during each study. Chest pain and S-T segment depression during exercise were highly reproducible: 7 of 9 had chest pain and 7 of 9 had S-T segment depression on both occasions. In only 1 patient did either endpoint differ; 1 patient had S-T depression in the second study, but not in the first.

During the pretreatment bicycle exercise test in the propranolol study group, 19 of the 22 patients had chest pain and 20 had S-T segment depression (Table I). Compared with the pretreatment study, medium-dose propranolol significantly decreased each parameter; 9

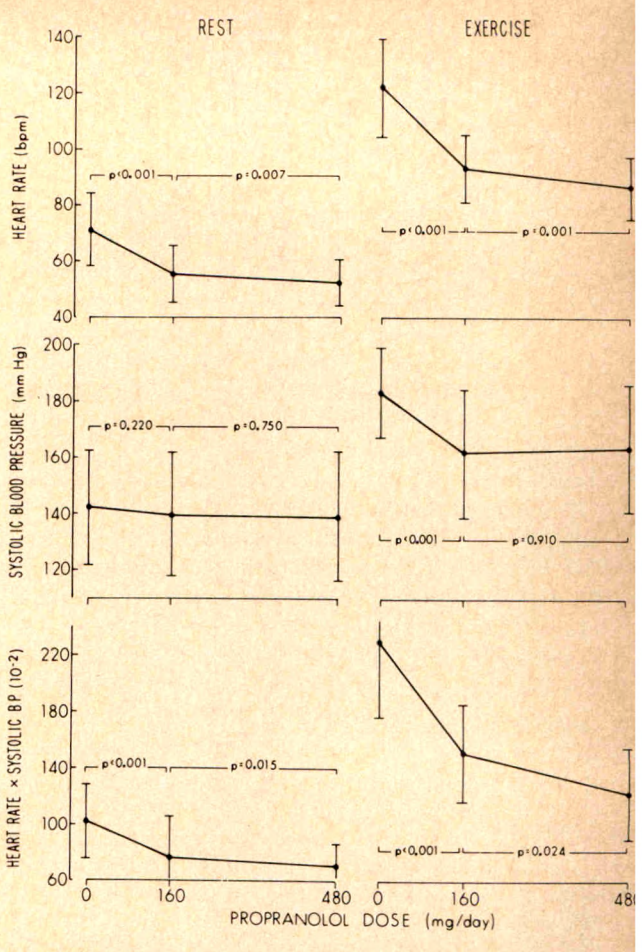

FIGURE 2. Effect of medium-dose (160 mg/day) and high-dose (480 mg/day) propranolol on heart rate (**upper panels**), systolic blood pressure (**middle panels**), and rate-pressure product. Exercise variables during propranolol therapy were measured at the pretreatment maximum work load. Data are shown as mean ± standard deviation. p values were derived from Wilcoxon signed rank tests (significant difference: p <0.03).

patients had chest pain (p = 0.002) and 10 had S-T segment depression (p = 0.002). High-dose propranolo showed a trend toward further improvement compared with the medium dose; 2 patients had chest pain (p = 0.014) and 4 had S-T segment depression (p = 0.049). Neither endpoint was present in 9 patients during medium-dose propranolol therapy and 18 patients during high-dose therapy. In these patients, exercise was limited by fatigue.

Propranolol had little effect on the maximum work load achieved during exercise testing. Three patients achieved an additional 150 kpm/min exercise work load with medium-dose propranolol, and another 7 patients were able to achieve a small additional increment of 100 kpm/min. With high-dose propranolol, only 2 patients increased their work load by 100 kpm/min compared with the medium dose. Exercise performance did not decrease in any patient.

Hemodynamic responses: In the 9 patients who exercised to a symptom-limited maximum on 2 occasions 1 to 2 weeks apart without receiving propranolol,

heart rate varied by 11 ± 8 beats/min at rest and by 8 ± 7 beats/min during exercise. Corresponding variations in systolic blood pressure were 11 ± 9 mm Hg and 8 ± 8 mm Hg, respectively.

The effects of medium-dose and high-dose propranolol on rest and exercise hemodynamic features are summarized in Figure 2. Medium-dose therapy effected a decrease in mean heart rate compared with pretreatment values from 71 to 55 beats/min (23%) at rest and from 122 to 93 beats/min (26%) during exercise ($p < 0.001$). Systolic blood pressure was not significantly affected at rest (mean 139 mm Hg compared with 142 mm Hg before treatment), but decreased slightly during exercise from 183 to 162 mm Hg ($p < 0.001$). High-dose as compared with medium-dose propranolol resulted in a small but significant additional decrease in heart rate. Resting heart rate decreased by 5% from 55 to 52 beats/min ($p = 0.001$) and exercise heart rate decreased by 7% from 93 to 86 beats/min ($p = 0.001$). Resting and exercise systolic blood pressure did not change further with high-dose therapy.

Coincident with the changes in heart rate and systolic blood pressure, medium-dose propranolol therapy decreased mean rate-pressure product by 25% from 102,000 to 76,000 at rest ($p < 0.001$) and by 34% from 229,000 to 151,000 during exercise ($p < 0.001$). High-dose propranolol caused a further small decrease in rate-pressure product, by 7% from 76,000 to 71,000 at rest ($p = 0.015$) and by 6% from 151,000 to 142,000 during exercise ($p = 0.024$).

Left ventricular function: Duplicate rest and exercise radionuclide studies performed in 9 patients demonstrated a high degree of reproducibility for estimates of EF and WMS. Differences between rest measurements were 0.021 ± 0.02 (standard deviation [SD]) for EF and 1.3 ± 1.0 for WMS; exercise values differed by 0.043 ± 0.044 for EF and 1.5 ± 1.1 for WMS.

Changes in rest and exercise EF during medium-dose and high-dose propranolol therapy are shown in Figure 3. Resting EF for the group did not change during treatment with either dose of propranolol; the mean value was 0.57 at each evaluation. Medium-dose propranolol resulted in a significant increase in exercise EF from 0.51 to 0.56 ($p = 0.025$); exercise EF increased by ≥0.08 (2 SD of the mean variability of the measurement) in 8 patients. No further increase in mean exercise EF resulted from the higher dose ($p = 0.095$); however, an absolute increase in exercise EF was seen in 16 patients compared with a decrease in only 5 patients, and exercise EF increased by ≥0.08 in an additional 3 patients compared with the medium-dose propranolol.

The change in EF during propranolol therapy was highly variable between patients. Figure 3 shows that subjects who had lower exercise EFs before therapy tended to have the greatest increases in exercise EF

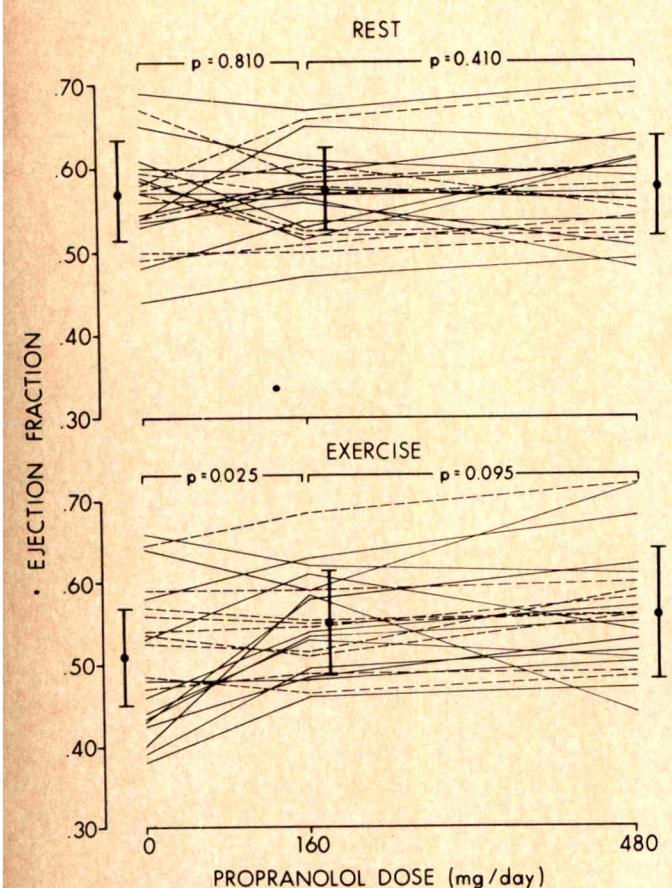

FIGURE 3. Changes in rest and exercise ejection fraction during medium-dose (160 mg/day) and high-dose (480 mg/day) propranolol therapy. Individual data are displayed for patients whose functional class improved (responders, **solid lines**) and for those in whom functional class did not improve (nonresponders, **broken lines**). **Bars** represent mean ± standard deviation. Analysis as in Figure 2.

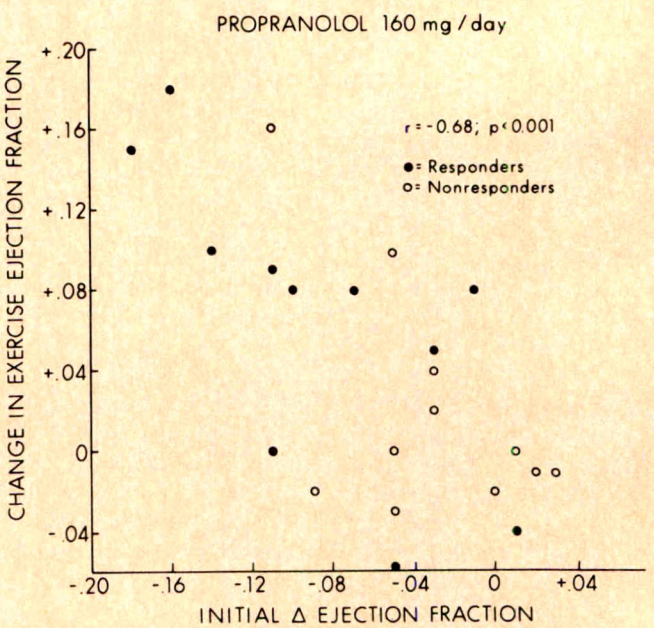

FIGURE 4. Relationship between pretreatment ejection fraction response to exercise (initial Δ ejection fraction) and change in exercise ejection fraction during medium-dose propranolol therapy. A marked initial decrease in ejection fraction was a significant univariate predictor of improvement in exercise ejection fraction with propranolol and of clinical response to therapy.

during therapy; of 11 patients whose pretreatment exercise EF was <0.05, the exercise EF increased in 9 during medium-dose propranolol therapy. Figure 4 illustrates the relationship between the pretreatment EF response to exercise and the change in exercise EF during medium-dose propranolol therapy, with $r = -0.68$, $p < 0.001$.

The relation between clinical response to medium-dose propranolol and the response of exercise-induced LV dysfunction is shown in Figures 3 and 4. Patients who improved by at least 1 functional class during the 2-week treatment period (solid lines in Figure 3, closed circles in Figure 4) demonstrated a greater decrease in EF during exercise before treatment, and a greater increase in EF during medium-dose propranolol than did patients who did not improve ($p < 0.03$, unpaired t test). Thus, 9 of 11 patients with exercise EFs <0.50 improved by 1 functional class; in 6 of these 9 patients exercise EF increased by ≥0.08.

Changes in EF between medium-dose and high-dose propranolol were small compared with the initial response to medium-dose therapy, and they were also variable. Two patients whose exercise EFs increased with medium-dose treatment demonstrated a decrease to the pretreatment level (by 0.07 and 0.14) with high-dose propranolol (Fig. 3). These changes were not accompanied by reversal of the improved wall motion seen in medium-dose therapy, suggesting a decrease in contractility in the normal or nonischemic segment.

Resting WMS did not change at either dose level of propranolol (Fig. 5). During exercise, WMS improved significantly during medium-dose propranolol therapy from 5.4 to 3.3 ($p = 0.001$); exercise WMS decreased by at least 2 (2 SD of the mean variability of the measurement) in 13 patients. The small difference in exercise WMS between medium-dose and high-dose therapy was not statistically significant for the group, but showed a trend toward further improvement ($p = 0.082$). This was supported by an absolute decrease in WMS in 9 patients compared with an increase in only 2 patients, and a decrease in WMS by ≥2 in an additional 2 patients.

Plasma propranolol levels: Plasma propranolol levels were obtained in all patients during medium-dose therapy and in 18 of 22 during high-dose therapy. A wide range of plasma propranolol levels was produced at each dose level of the drug; plasma propranolol ranged from 10 to 125 ng/ml during medium-dose therapy and from 61 to 525 ng/ml during high-dose therapy. In all except 1 patient who had plasma propranolol estimates at both dose levels, the value was higher with high-dose therapy than with medium-dose therapy. The 2 patients whose exercise EFs decreased to pretreatment values at the higher dose had serum levels of 83 and 267 ng/ml.

In an attempt to relate plasma propranolol levels to the extent of beta-blockade, the relationship between plasma propranolol and the percent reduction in exercise heart rate was examined (Fig. 6). Consistent with the findings of other investigators,[3,4,6] the relationship

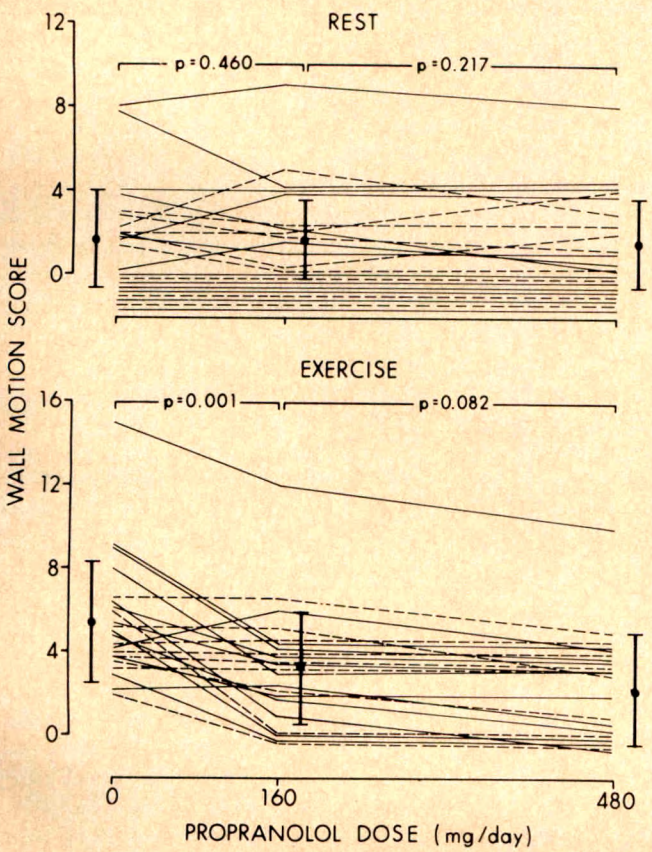

FIGURE 5. Changes in rest and exercise wall motion score during medium-dose and high-dose propranolol therapy. Data are represented as in Figure 3.

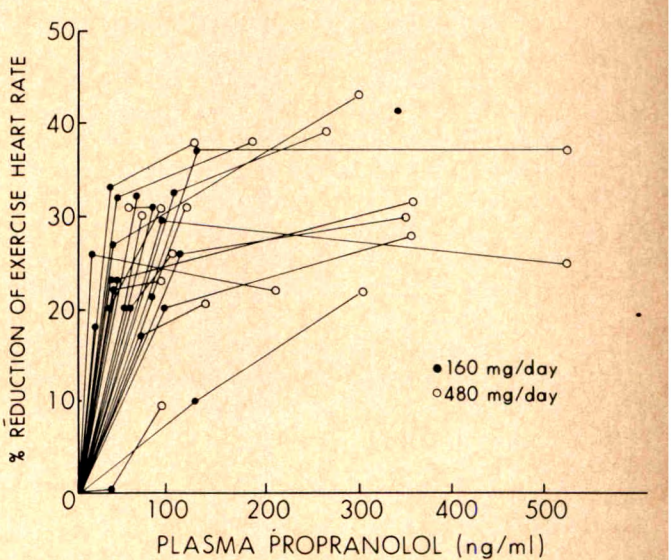

FIGURE 6. Relationship between plasma propranolol level and the degree of beta-adrenergic blockade as assessed by percent reduction of exercise heart rate. Medium-dose propranolol (160 mg/day, **closed circles**) produced plasma levels ranging from 10 to 125 mg/ml, and reduced exercise heart rate by approximately 25%. High-dose propranolol (480 mg/day, **open circles**) achieved plasma levels >200 mg/ml in many patients but had only a small additional beta-blocking effect.

between plasma propranolol and the percent reduction in exercise heart rate appeared exponential. Medium-dose propranolol produced substantial beta-blockade, consistent with the observed effects described earlier and represented in Figure 2. Linear regression analysis of the relationship between log plasma propranolol level and percent reduction in exercise heart rate at the 2 dose levels revealed a weak but significant relationship ($r = 0.36$, $p = 0.03$). Changes in exercise EF and WMS were not significantly related to log plasma propranolol ($r = 0.20$ and -0.19, respectively).

Discussion

These data demonstrate that most of the effects of propranolol on hemodynamic determinants of myocardial oxygen demand such as heart rate, blood pressure, and rate-pressure product, and on functional indexes of LV ischemia such as global EF and regional wall motion, are seen with a moderate dose. Although high-dose propranolol produced only a slight additional effect on these measured parameters, there was a significant further reduction in exercise chest pain and S-T segment depression; several patients further improved their functional class, and no patient experienced a deterioration of LV function with the high dose.

The beneficial effect of high-dose propranolol on anginal symptoms appears to support earlier observations by Prichard,[3] and Alderman,[4] and their co-workers that improvement in the control of exertional angina was progressive as dosage increased to levels equivalent to the higher dose used in our study. However, the changes in heart rate and blood pressure observed in the present study indicate that only minor additional beta-blockade resulted from the higher dose. The apparent discrepancy between clinical symptoms and hemodynamic effects may be explained by the patterns of physical activity that produce angina in patients with ischemic heart disease. In chronic stable angina, patients establish a habitual level of activity that corresponds to their pain threshold. Unless a conscious attempt is made to markedly increase that activity level, a small change in the threshold of angina may dramatically reduce the number of anginal attacks. Indeed, increases in objective measurements of exercise capacity in the studies cited above and in the present study were much smaller than the clinical improvement with high-dose therapy would suggest.

A further apparent inconsistency that requires consideration is that high-dose as compared with medium-dose propranolol significantly reduced chest pain and S-T segment depression, but effects on exercise-induced LV dysfunction were not significant for the group. First, it should be noted that there was not a major qualitative difference between these observations; changes in LV function were nearly significant for the group, and LV function did improve in the majority of patients with the higher dose. It is unlikely that functional changes were intrinsically less sensitive to ischemia than chest pain or electrocardiographic changes. Upton et al[14] observed that LV dysfunction often appeared before the onset of chest pain and S-T segment depression. The most likely explanation for the apparently inconsistent finding is the method used to record variables during the exercise test. Chest pain and S-T depression were used to determine endpoints of exercise and were recorded as binary variables; thus, small decreases in ischemia may result in highly significant decreases in the incidence of these parameters. In contrast, EF and WMS were not used as exercise endpoints and were quantitated as continuous variables; it follows that statistical analysis would be relatively insensitive to small changes in these measurements.

Changes in global EF must be interpreted in the light of differential effects of propranolol in normal and ischemic myocardium. Previous studies have demonstrated that propranolol in normal, young healthy subjects decreases exercise EF.[15] Theroux et al[16] observed in conscious dog preparations that propranolol improved wall contraction in ischemic regions, but decreased contraction in normal or nonischemic myocardium. Thus, in the presence of exercise-induced ischemia in man, propranolol may be expected to reduce contraction of nonischemic regions and increase contraction in ischemic regions. The effects on global EF will represent the net of these differing effects. An increase in EF during exercise after propranolol is likely to be due to improved function in the ischemic region; on the other hand, an unchanged exercise EF may result from improved function in an ischemic region which is cancelled by reduced function in the nonischemic areas. In the present study, the patients with the lowest exercise EFs and presumably the greatest amount of exercise-induced ischemia had the greatest increases in global EF during propranolol therapy. Two of 3 patients with exercise EF >0.60 actually decreased exercise EF with moderate-dose propranolol; these patients did not have a corresponding increase in WMS, indicating that the decrease in EF was due to an effect on nonischemic myocardium. The effects of propranolol on WMS were more consistent; in all but 1 patient, WMS either decreased or remained unchanged with moderate-dose propranolol. Consistent with the EF changes, subjects with higher exercise WMS tended to have the greatest decreases with propranolol.

In selecting an appropriate regimen of drug therapy, the benefits derived from increased dosage must be balanced against the potential disadvantages. In the case of propranolol, caution has been advised in the use of large doses because of possible depression of LV function. Epstein et al[17] have emphasized that the sympathetic nervous system plays an important part in the contractile response of the left ventricle to exercise, and it is possible that this is especially important in patients who have comprised LV function. The view that beta-adrenergic blockade may cause depression of LV function has been supported by the studies of Frishman,[7] Helfant,[18] Coltart,[19] and their co-workers, which demonstrated a decrease in various indexes of resting LV contractility in many patients after administration of increasing doses of propranolol. Despite these observations, data from the present study demonstrated no overall decrease in the LVEF with either medium-dose or high-dose propranolol; in fact, exercise LV function as determined by EF increased slightly in

most patients even with high-dose propranolol. These results support our own clinical impression that high-dose propranolol does not induce heart failure in patients with angina and normal or near-normal LV function at rest. However, they should not be extrapolated to patients who have LV dysfunction, since only 4 of our 22 subjects had a resting EF <0.50, and no subject had symptoms of heart failure.

A weak relation was seen in the present study between plasma levels of propranolol and exercise heart rate ($r = 0.36$), exercise EF ($r = 0.20$), and exercise WMS ($r = -0.19$). This is at least partially explained by the known dose-response relationship of the drug. As demonstrated by Coltart and Shand,[6] near maximal beta-blockade is produced by small doses of propranolol with correspondingly low plasma levels; both medium-dose and high-dose propranolol as used in the present study produce blood levels that lie on the plateau of the dose-response curve. The relationship between plasma levels and drug effect may be further weakened by the fact that propranolol's action involves the competitive blockade of a highly variable physiologic system. Thus, a variable response to the drug may reflect differences in sympathetic activity, independent of the blood level of the drug.

The results of this study support the use of high doses of propranolol in patients with exertional angina who fail to respond adequately to medium-dose therapy. Despite only a small additional effect on hemodynamic features and quantitative indexes of myocardial ischemia, high-dose propranolol may be of additional benefit in relieving ischemia and improving symptoms, without a significant risk of inducing LV failure in subjects with normal or near normal LV function.

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Anatomic and Prognostic Significance of New T-Wave Inversion in Unstable Angina

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The significance of the development of new T-wave inversion was studied in 118 consecutive patients with unstable angina. The electrocardiograms during hospitalization in the coronary care unit were analyzed for occurrence of new T-wave inversion ≥2 mm and correlated with findings at coronary angiography (73 patients) and at follow-up (112 patients). Twenty-nine patients had anterior T-wave inversion. Of these, 25 patients (86%) had ≥70% diameter reduction of the left anterior descending (LAD) artery, compared with 11 (26%) of 42 patients without anterior T-wave inversion ($p < 0.001$). The sensitivity of T-wave inversion for significant LAD stenosis was 69%, specificity 89%, and positive predictive value 86%. Two patients had T-wave inversion in the inferior leads. Both patients had significant right coronary artery disease, compared with 18 of 55 patients without inferior T-wave inversion (difference not significant [p = NS]. Seventy-one patients who were treated medically had 16 ± 9 months' follow-up. Of 26 patients who had T-wave inversion, 10 (38%) had cardiac events, compared with 7 (16%) of the remaining 45 patients without T-wave inversion ($p < 0.05$). Forty-one patients who had undergone coronary bypass surgery had 19 ± 9 months' follow-up. Of 22 patients with T-wave inversion, 4 (18%) had cardiac events, compared with 2 (11%) of the remaining 19 patients without T-wave inversion (p = NS).

Thus, development of new T-wave inversion ≥2 mm in patients with unstable angina (1) is predictive of significant coronary artery stenosis, and (2) identifies a subgroup with poor prognosis when treated medically.

During hospital observation, patients with unstable angina may develop new T-wave inversion on the electrocardiogram, without associated increase and decrease of cardiac enzymes. Although transient ST-T segment changes during episodes of angina pectoris are well recognized as reflections of acute myocardial ischemia,[1–8] the significance of the gradual development of T-wave inversion associated with symptoms of unstable angina is less well understood. Recently, it has been suggested that this characteristic electrocardiographic pattern is associated with a particularly poor prognosis.[9] The purpose of the present study was 2-fold: (1) to define the pathoanatomic correlation of new T-wave inversion in patients with unstable angina, in particular the distribution and severity of coronary artery disease; and (2) to analyze the potential prognostic implications of this finding in medically and surgically treated patients.

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Methods

Patient group: The electrocardiograms and medical records of 146 consecutive patients, discharged from the coronary care unit in the period from March 1980 to August 1982 with the diagnosis of unstable angina, were reviewed. Unstable angina was defined as new or recent (<1 month) onset of typical angina pectoris brought on by minimal exertion or at rest, or recent exacerbation of previously stable typical exertional angina pectoris.

All patients were in the coronary care unit for at least 48 hours. Cardiac enzymes (creatine kinase, creatine kinase isoenzymes, lactic dehydrogenase isoenzymes, and serum glutamic oxaloacetic transaminase) were obtained on admission and every 6 hours for 48 hours. No patient had enzymatic documentation of myocardial infarction (MI) according to the criteria of the New York Heart Association.[10]

Twenty-eight patients were excluded from further analysis: 12 patients who had had acute MI <2 weeks before readmission to the coronary care unit, 14 patients with either complete left or right bundle branch block, and 1 patient with previous transmural anterior and inferior MI. The remaining 118 patients are the study group.

Treatment groups: The patients were classified into 3 groups: Group A, 42 patients (28 men, 16 women, mean age 60 years) who underwent coronary angiography and subsequently had coronary artery bypass surgery; Group B, 31 patients (16 men, 15 women, mean age 56 years) who also underwent coronary angiography but were subsequently treated medically because findings at coronary angiography revealed either nonsurgical coronary artery disease, insignificant coronary artery disease, or normal coronary arteries; and Group C, 45 patients (34 men, 11 women, mean age 62 years) who did not undergo coronary angiography for reasons of age, resolution of symptoms after intensive medical therapy with nitrates, beta-blocking agents, and/or calcium-channel blocking drugs, or presence of underlying disease that precluded surgery. It should be emphasized that because of the retrospective nature of the present study, allocation of patients to each treatment group was not affected by the presence or absence of T-wave inversion on the electrocardiogram.

Electrocardiograms: All 12-lead electrocardiograms were obtained using standard lead placement and either a Cambridge model 3038/2S or model VS 4 electrocardiographic recorder (Cambridge Instruments, Ossining, New York). Serial electrocardiograms were obtained on admission to the coronary care unit and daily thereafter for at least 2 days. Supplemental electrocardiograms were obtained during episodes of chest pain. The electrocardiographic T-wave inversion analyzed in the present study fulfilled all of the following criteria: (1) a new finding on or after coronary care unit admission in comparison to previous electrocardiograms (patients without previous electrocardiograms for comparison were not entered in the study, unless they presented with new symptoms of unstable angina); (2) a sustained (>24 hours) electrocardiographic finding, that is, not a transient phenomenon associated with pain only; (3) ≥2 mm in amplitude from the isoelectric line; (4) T-wave inversion present in ≥2 of the anterior leads (I, aVL, V2 to V6) and/or in ≥2 of the inferior leads (II, III, and aVF), without evidence of previous MI in the leads analyzed.

Evidence of previous anterior MI was defined as presence of Q waves >0.04 second duration in any of leads I, aVL, and V_2 to V_6, and of previous inferior MI as a presence of Q wave >0.03 second duration in lead II or aVF.[10]

The electrocardiograms were analyzed independently by 2 observers without knowledge of coronary angiographic findings or clinical outcome. Between the 2 observers, complete agreement existed on 115 of 118 electrocardiograms. On the remaining 3, a consensus was reached.

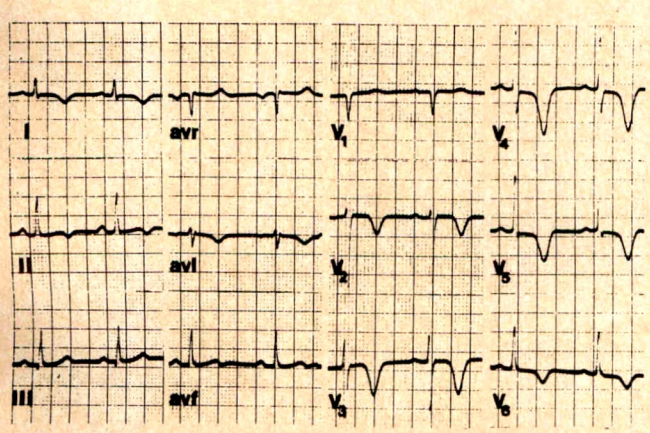

FIGURE 1. Symmetrical T-wave inversion with isoelectric S-T segment.

Electrocardiographic study groups: In the present study, the significance of the presence or absence of new T wave inversion was evaluated only in leads without evidence of previous MI. Electrocardiographic evidence of previous anterior MI was present in 8 patients, and of previous inferior MI in 21 patients. Therefore, the anterior leads were examined in a total of 110 patients (41 in Group A, 30 in Group B, and 39 in Group C), whereas the inferior leads were examined in a total of 97 patients (34 in Group A, 23 in Group B, and 40 in Group C).

Coronary angiography: Coronary angiography was performed using the Judkins or Sones technique. Multiple projections of selective coronary angiograms were obtained. Arteriograms were analyzed by at least 2 independent experienced observers without knowledge of electrocardiographic findings. Significant stenosis of a coronary artery was defined as ≥70% reduction of the luminal diameter determined by visual inspection. The dominant coronary artery supplying the inferior wall was noted. Left anterior descending (LAD) disease in the present study is defined as disease of the LAD or a major diagonal branch supplying blood flow to the anterior wall of the left ventricle.

Follow-up: Follow-up data on patients were obtained from private physicians' records, hospital records, or telephone interviews with the patients. MI during the follow-up period was defined as enzymatically and/or electrocardiographically documented MI. Death was assumed to be of cardiac origin if it was instantaneous, if the patient had complained of chest pain immediately before death, or if the patient died of cardiogenic shock or arrhythmia in a post-MI course.

Statistical methods: Statistical analysis was performed using the chi-square test. For analysis of series of proportions, the test for linear trend among proportions was utilized.[11] A p value <0.05 was considered statistically significant. Sensitivity is defined as true positives (TP) divided by false negatives (FN) + TP × 100; specificity is defined as true negatives (TN) divided by TN + false positives (FP) × 100; positive predictive value is defined as TP divided by TP + FP × 100.

Results

Electrocardiography: Overall, new T-wave inversion ≥2 mm occurred in 47 (40%) of 118 patients. Twenty patients had normal electrocardiograms on admission and subsequently developed T-wave inversion. In the remaining 27 patients, T-wave inversion was either a definite new finding compared with a recent electrocardiogram (15 patients), or was considered a new finding because the symptoms of unstable angina occurred anew (12 patients). The prevalence of new T-wave inversion was not significantly different among the 3 patient treatment groups: 20 (47%) of 42 patients in Group A, 11 (35%) of 31 patients in Group B, and 16 (36%) of 45 patients in Group C (p = NS). Of the 110 patients without previous anterior MI, new anterior T-wave inversion occurred in 41 (37%). Of the 97 patients without previous inferior MI, new inferior T-wave inversion occurred in 6 (6%) patients. Three predominant configurations of T-wave inversion were observed, although transition from one form to another on the same or serial electrocardiograms was noted. The most common form was symmetrical inversion with isoelectric S-T segment (Fig. 1). The second form was biphasic with the inverted portion >2 mm from the

isoelectric line (Fig. 2). Finally, T-wave inversion was noted in association with S-T segment depression (Fig 3).

Coronary angiography: Of the 73 patients who underwent coronary angiography (Group A and B), 56 had ≥70% stenosis of 1 or more coronary arteries. Twenty-seven had single-vessel, 15 had double-vessel, and 14 had triple-vessel disease. Of the remaining 17 patients, 3 patients had 50 to 70% stenosis of a single coronary artery, 2 patients had <50% stenosis of 1 vessel, and 12 patients had no evidence of coronary artery disease. Two patients had previous anterior MI, and 16 patients had previous inferior MI. The 31 patients comprising Group B were not considered for surgery for varying reasons. Fifteen patients had insignificant coronary artery disease and 8 patients had single-vessel disease only. Three patients had double-vessel disease and 5 patients had triple-vessel disease; however, they had such severe distal disease that grafting was judged not technically feasible.

New T-wave inversion and coronary artery anatomy: Thirty-one of the patients who had coronary angiography had new T-wave inversion, 27 (87%) of these had significant coronary artery disease, compared with 26 of 42 patients without new T-wave inversion ($p < 0.01$).

Anterior T-wave inversion: New T-wave inversion in the anterior leads was evaluated as a predictor of LAD disease in 71 patients without previous anterior MI. Of 29 patients with new T-wave inversion, 25 (86%) had ≥70% stenosis of the LAD. Of 42 patients without new T-wave inversion, only 11 (26%) had significant LAD stenosis ($p < 0.0001$) (Fig. 4). For the detection of LAD disease, the anterior leads V_2 to V_6 were most important: no patients with T-wave inversion in lead I or aVL had normal anterior leads. Thus, new T-wave inversion ≥2 mm in the anterior leads had a positive predictive value of 86% (25 of 29), a sensitivity of 69% (25 of 36), and a specificity of 89% (31 of 35) for significant LAD disease.

Four patients who had new T-wave inversion had no significant LAD disease. Three of these had normal coronary arteries. All had resolution of their anginal symptoms in the follow-up period without any antianginal medical therapy. The remaining patient had significant narrowing of the left circumflex artery. During the 28 month follow-up period, this patient continued to have anginal symptoms, despite eventual single-vessel coronary artery bypass grafting.

Inferior T-wave inversion: New T-wave inversion in the inferior leads was analyzed as a predictor for dominant right coronary artery or dominant left circumflex artery disease in 57 patients without previous inferior MI. Only 2 of 57 patients had new T-wave inversion. Both had ≥70% stenosis of the dominant artery supplying the inferior wall of the left ventricle. In comparison, 18 of 55 patients without inferior lead T-wave inversion had comparable significant disease (p = NS). Thus, although new T-wave inversion in the inferior leads appears to be specific for dominant right coronary artery or left circumflex artery disease, the sensitivity is low (10%).

Amplitude of T-wave and severity of stenosis: As discussed earlier, of 42 patients without T-wave inversion in the anterior leads, 11 patients (26%) had ≥70% LAD stenosis. In contrast, of 29 patients with ≥2 mm T-wave inversion in the anterior leads, 25 (86%) had significant LAD disease. Of 21 patients with ≥3 mm T-wave inversion, 17 (81%) had significant LAD stenosis, and 13 (81%) of 16 patients with ≥4 mm T-wave inversion had this finding (p = NS). Thus, an increased amplitude of negative T waves was not associated with higher prevalence of disease. Similarly, no correlation existed between the amplitude of negative T waves and the severity of LAD stenosis. Greater than 90% stenosis of the LAD artery occurred in 9 (66%) of 29 patients with ≥2 mm T-wave inversion, in 13 (62%) of 21 patients with ≥3 mm T-wave inversion and 12 (75%) of 16 patients with ≥4 mm T-wave inversion (p = NS).

New T-wave inversion and number of diseased coronary arteries: New T-wave inversion in the anterior leads correlates well with the presence of significant LAD disease. Of a total of 71 patients, 36 had LAD disease. Of these, 10 of 14 patients with single-vessel LAD disease, 4 of 9 patients with double-vessel disease, and 11 of 13 patients with triple-vessel disease had new T-wave inversion in the anterior leads (p = NS). Thus,

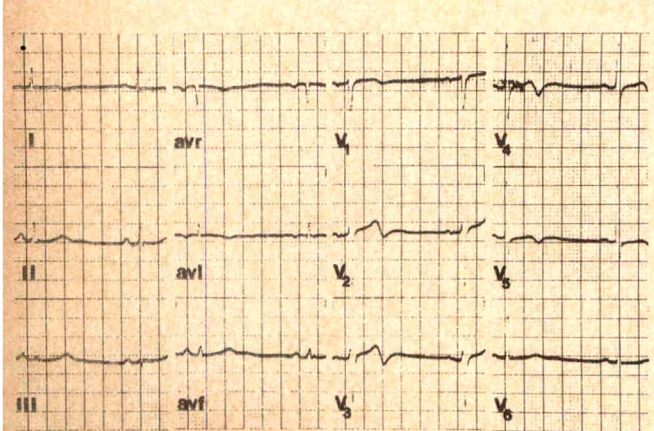

FIGURE 2. Biphasic T-wave inversion.

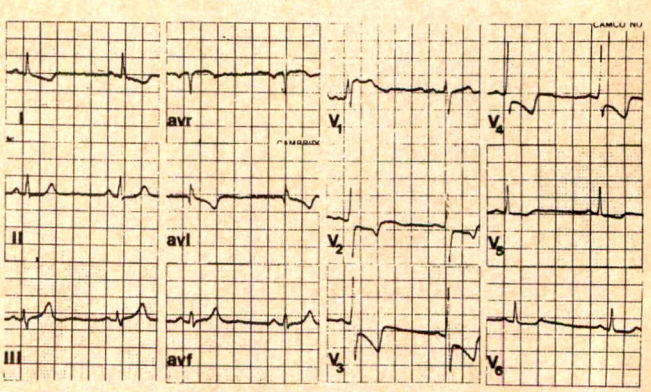

FIGURE 3. T-wave inversion associated with S-T segment depression.

the presence of new T-wave inversion is not predictive for number of vessels involved.

Follow-up: *Medical treatment:* A total of 76 patients (Groups B and C) were treated medically with beta-adrenergic blocking agents, nitrates, and/or calcium channel antagonists. Five patients were lost to follow-up. The remaining 71 patients had follow-up for 16 ± 9 months. Twenty-six patients had new T-wave inversion: 20 in anterior leads, 4 in inferior leads, and 2 in both anterior and inferior leads. During the follow-up period, 10 (38%) of 26 patients had either acute MI (3 patients) or cardiac death (7 patients, 27%). Of these 10 patients, 6 had anterior T-wave inversion, 3 inferior T-wave inversion, and 1 both inferior and anterior T-wave inversion. In contrast, only 7 (16%) of 45 patients without new T-wave inversion on the electrocardiogram during the hospital stay had acute MI (4 patients) or cardiac death (3 patients) during the follow-up period ($p < 0.05$) (Fig. 4). The mean length of time between coronary care unit hospitalization and cardiac event in follow-up was 6 ± 3 months in the 10 patients with new T-wave inversion, and 14 ± 6 months in the 7 patients without new T-wave inversion.

Coronary bypass surgery: Of 42 patients who underwent coronary bypass surgery (Group A), 1 was lost to follow-up and the remaining 41 patients had 19 ± 9 months (mean ± standard deviation) follow-up. During the preoperative stay in the coronary care unit, 22 patients had new T-wave inversion (20 in anterior leads and 2 in inferior leads). Four (18%) of the patients with T-wave inversion had either MI (2 perioperative and 1 seven months after operation) or cardiac death (1 perioperative). Of 19 patients without T-wave inversion, 2 (11%) had perioperative MI (p = NS). The incidence of cardiac events was not different (p = NS) from that in patients without T-wave inversion who were treated medically.

Discussion

The results of our study indicate that, among patients with unstable angina, the electrocardiographic development of new T-wave inversion in the anterior leads identifies a subgroup of patients with high prevalenc of significant LAD stenosis. Also, the subgroup with nev T-wave inversion appears to be at high risk for subse quent MI and cardiac death. A high incidence of cardia events occurred in patients who initially seemed to re spond favorably to intensive medical treatment. Ou findings corroborate in a larger group of patients, witl and without new T-wave inversion, the prognostic in formation to be gained from the surface electrocardio gram as reported by Zwaan et al.[9] These investigator included only patients with T-wave inversion in pre cordial leads V_2 and V_3, which may in part explain th lower prevalence (18%) of T-wave inversion and th extremely high incidence (70%) of cardiac events compared with that in our series.

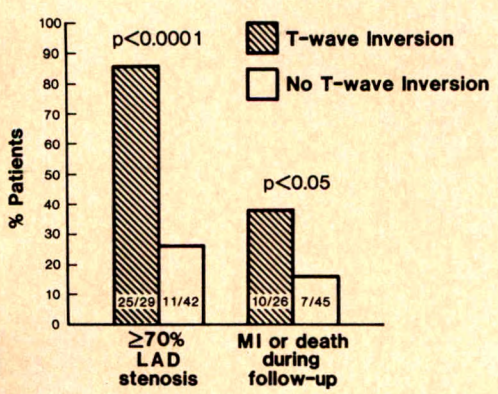

FIGURE 4. Prevalence of significant left anterior descending coronary artery stenosis and the incidence of cardiac events in patients with and without new T-wave inversion. LAD = left anterior descending coronary artery; MI = myocardial infarction.

Previous studies on unstable angina, as a rule, eithe did not separately analyze the patients with T-wav inversion and/or required electrocardiographic change as entrance criteria to their study group.[1–8,12] Currently the management of individual patients with unstabl angina may vary considerably in different centers. Ir some, immediate coronary angiography and grafting o the coronary arteries is recommended, whereas in other a more conservative attitude is taken. As a rule, th electrocardiogram is employed only as additional ob jective clinical evidence of myocardial ischemia wher transient ST-T segment changes occur, particularly during pain. The decision to proceed with coronary angiography and subsequent coronary bypass surgery usually is predominantly based on failure of medica treatment, rather than electrocardiographic findings The potential prognostic value of electrocardiograms in patients with unstable angina only recently has beer appreciated.[8,9,13] Our study demonstrates that not only deep negative T waves (Fig. 1) but also less impressive T-wave inversions correlate with significant stenosis o the LAD.

New negative T-wave inversion in the inferior leads occurred less frequently in our study and appeared to have less clinical value than precordial T-wave changes Nevertheless, the 2 patients with new T-wave inversion in the inferior leads both had significant stenosis of the dominant artery supplying the inferior wall. This ap pears to indicate that the electrocardiographic location of new negative T-wave inversion correlates with the anatomic location of severe coronary artery stenosis The underlying pathophysiologic mechanism of the occurrence of electrocardiographic negative T waves is incompletely understood. Reversible electrocardio graphic findings associated with ischemia are often thought of as transient phenomena that resolve imme diately as ischemia is diminished. Myocardial ischemia involving the subepicardial area may alter and reverse the pathway of electrical repolarization resulting in inverted T-wave morphology.[14,15] The fact that the T-wave inversion lingers after resolution of symptoms implies structural or biochemical alteration of the myocardium.

Myocardial perfusion defects on thallium-201 scintigrams, suggesting myocardial ischemia, have been demonstrated in 40% of patients with unstable angina even during the pain-free period.[16] Donsky et al[17] re-

ported abnormal technetium-99m–pyrophosphate myocardial scintigrams in approximately one third of patients with unstable angina in the absence of enzymatic or electrocardiographic evidence of acute MI. Clinical-pathologic correlation in these patients demonstrated scattered foci of myocardial necrosis.[18] In patients with unstable angina the distinction between severe ischemia and small nontransmural MI is an artificial one. In this light, the poor long-term prognosis of patients with new T-wave inversion in unstable angina is similar to that of patients with nontransmural MI, who have increased posthospital discharge mortality and complications.[19,20]

Clinical implications: A recent report of a prospective study by Hultgren et al[21] examining medical versus surgical therapy in unstable angina showed a small improvement in survival of those undergoing coronary artery bypass surgery compared with those receiving medical therapy. Early cardiac catheterization and surgery in patients with unstable angina is being advocated by some groups.[22,23] There clearly is a need to define more precisely high-risk subgroups that could benefit most from surgery.

In patients with unstable angina, the development of new T-wave inversion on the electrocardiogram provides important prognostic information, heralding increased incidence of MI and cardiac death. Although the number of patients is relatively small and bias in patient selection cannot be excluded, the significantly lower incidence of cardiac events in patients who underwent coronary bypass surgery, compared with that in patients treated medically, suggests that this subgroup in particular benefits from a more aggressive approach. Further studies should explore results of medical versus surgical therapy in this high-risk subgroup.

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New and important evidence affirms the

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New endoscopic studies show:

No significant difference in GI lesions between

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and

Micro-K®
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SLOW-K: UNSURPASSED FOR SAFETY AMONG SLOW-RELEASE KCl CAPSULES OR TABLETS

Maximum-dosage (96 mEq) multistudy data*

Results: No significant differences in endoscopic changes found between Slow-K and Micro-K at 96-mEq dosage.†

(Administered as four 8-mEq tablets or capsules, t.i.d.)

These data resulted from four different studies (involving 64 subjects) that used the maximum recommended daily dosage of 96 mEq before food ingestion and with concomitant administration of the maximum recommended dosage of the anticholinergic agent glycopyrrolate (6 mg).[1-4]

Maximum-dosage multistudy data

					Endoscopic findings ‡			
N	Treatment	Daily dosage	Glycopyrrolate	Food	Ulcers	3	2	1
27	Slow-K	96 mEq	6 mg	No	1	1	6	12
37	Micro-K	96 mEq	6 mg	No	2	1	2	9

Results from similar studies supported by the A.H. Robins Company have shown a greater incidence of endoscopically observed GI irritation with Slow-K as compared to Micro-K when maximum doses of glycopyrrolate are administered.[5,6] These results, showing a significant difference between the products, are *inconsistent* with the data described herein, which do not show a significant difference.

High-dosage (48 mEq) multistudy data*

Results: No ulcers found with Slow-K or Micro-K. No significant differences in endoscopic changes found with Slow-K and Micro-K at 48-mEq dosage.

(Administered as two 8-mEq tablets or capsules, t.i.d.)

These data resulted from two different studies (involving 36 subjects) that used the high (48 mEq) dosage with food ingestion, and with and without the maximum recommended dosage of the anticholinergic agent glycopyrrolate. (Note: Glycopyrrolate was used in only one group of subjects on Slow-K.)[1,2] This 48-mEq dosage is higher than that normally used prophylactically.

High-dosage multistudy data

					Endoscopic findings ‡			
N	Treatment	Daily dosage	Glycopyrrolate	Food	Ulcers	3	2	1
12	Slow-K	48 mEq	6 mg	Yes	0	0	2	6
12	Slow-K	48 mEq	None	Yes	0	0	0	4
12	Micro-K	48 mEq	None	Yes	0	0	1	5

*These studies were conducted by Drs. D. Patterson and G. Jeffries of the Hershey Medical Center, and by Dr. D. Earnest of the University of Arizona (Tucson).

†Also included in these multistudy data were an additional 70 subjects taking an 8-mEq sustained-release KCl capsule, a K^+ elixir, a sustained-release KCl tablet of higher mEq dosage than that currently available, or a placebo. The elixir and the placebo did not produce any endoscopic changes greater than two Grade 1 and five Grade 1 endoscopic findings, respectively. The higher dose sustained-release KCl tablets produced two ulcers, two Grade 2 and six Grade 1 endoscopic findings. The 8-mEq sustained-release capsule produced two Grade 2 and two Grade 1 findings. All Grade 1 endoscopic changes were considered clinically meaningless.

‡Grade 0 = no endoscopic findings
1 = hyperemia and/or edema (the medical consensus is that this category is clinically meaningless)
2 = few erosions
3 = numerous erosions (>3)
4 = ulceration
5 = multiple ulcerations

The anticholinergic agent glycopyrrolate was given to slow gastric emptying, thus ensuring maximum contact of the KCl supplements with the gastric mucosa. The impact, if any, of high-dose glycopyrrolate on the gastric mucosa is unknown.

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CIBA

New epidemiologic study shows:

No difference between

Slow-K®

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use and no K^+ therapy in the incidence of upper GI bleeding in a hospital setting.

SLOW-K: UNSURPASSED FOR SAFETY AMONG SLOW-RELEASE KCl CAPSULES OR TABLETS

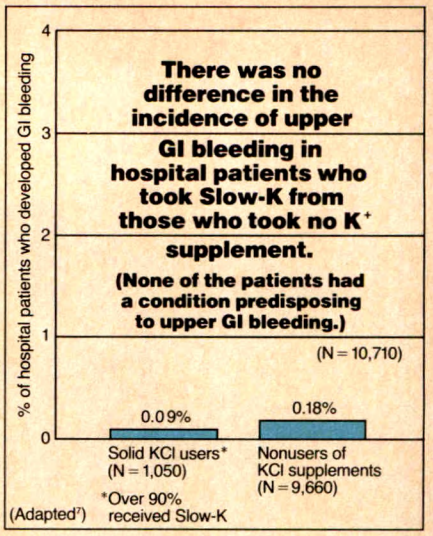
Experience of the Boston Collaborative Drug Surveillance Program[7]
As reported by Aselton and Jick in *Lancet,* January 22, 1983

Purpose of epidemiologic study:
To evaluate the relation between the use of wax-matrix KCl and the development of upper GI bleeding while in the hospital.

Patient population:
A total of 15,791 medical inpatients. Of those, 10,710 had no condition predisposing to upper GI bleeding. Of those, 1,050 received solid KCl* by mouth; 9,660 received no solid KCl.

Findings:
Of the 1,050 KCl users, 1 had GI bleeding (0.09%).
Of the 9,660 nonusers, 17 had GI bleeding (0.18%).

*Over 90% of this group received KCl in the form of Slow-K tablets.



(Adapted[7])

Conclusion: "These findings argue against a positive association between wax matrix KCl use and upper gastrointestinal bleeding over a short period of time."[7]

These new data are consistent with the overwhelming evidence compiled in 8 years of use with Slow-K® potassium chloride slow-release tablets 8 mEq.

Analysis of 5.6 million U.S. patient-years' data: approximately one GI lesion per 100,000 patient-years—and this incidence rate has remained unchanged since Slow-K was introduced in 1975.[8]

*Method of determining incidence:
A: Includes all cases (most conservative method)
B: Excludes cases in which causality was unlikely and/or Slow-K was contraindicated
C: Excludes cases in which B was present *and* in which data were insufficient to assess causality (least conservative method)

Summary of lesion incidence rates per 100,000 patient-years

	Method* A	B	C
Esophagus	0.14	0.02	0.02
Stomach	0.27	0.14	0.11
Duodenum	0.12	0.05	0.05
Small bowel/large bowel; unknown location	0.82	0.43	0.27
Total	1.36	0.64	0.44

(Adapted[8])

Conclusion: Slow-K is a safe agent.

Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

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- Over 2 million additional patients in 1982 alone
- Over 51.8 million new and refill prescriptions
- 8 years' U.S. clinical experience
- 17 years' worldwide clinical experience
- 5.6 million U.S. patient-years of use
- Listed on 80-85% of the larger U.S. hospital formularies

(Data on file, CIBA Pharmaceutical Company.)

Do you have any questions concerning Slow-K? A member of the CIBA medical staff would be happy to answer them.

Please write to:
Dr. Richard H. Roberts
Director of Professional Affairs
CIBA Pharmaceutical Company
556 Morris Avenue
Summit, New Jersey 07901

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SLOW-K®
potassium chloride **slow-release tablets**

Brief Summary of Prescribing Information

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev. 1/83)

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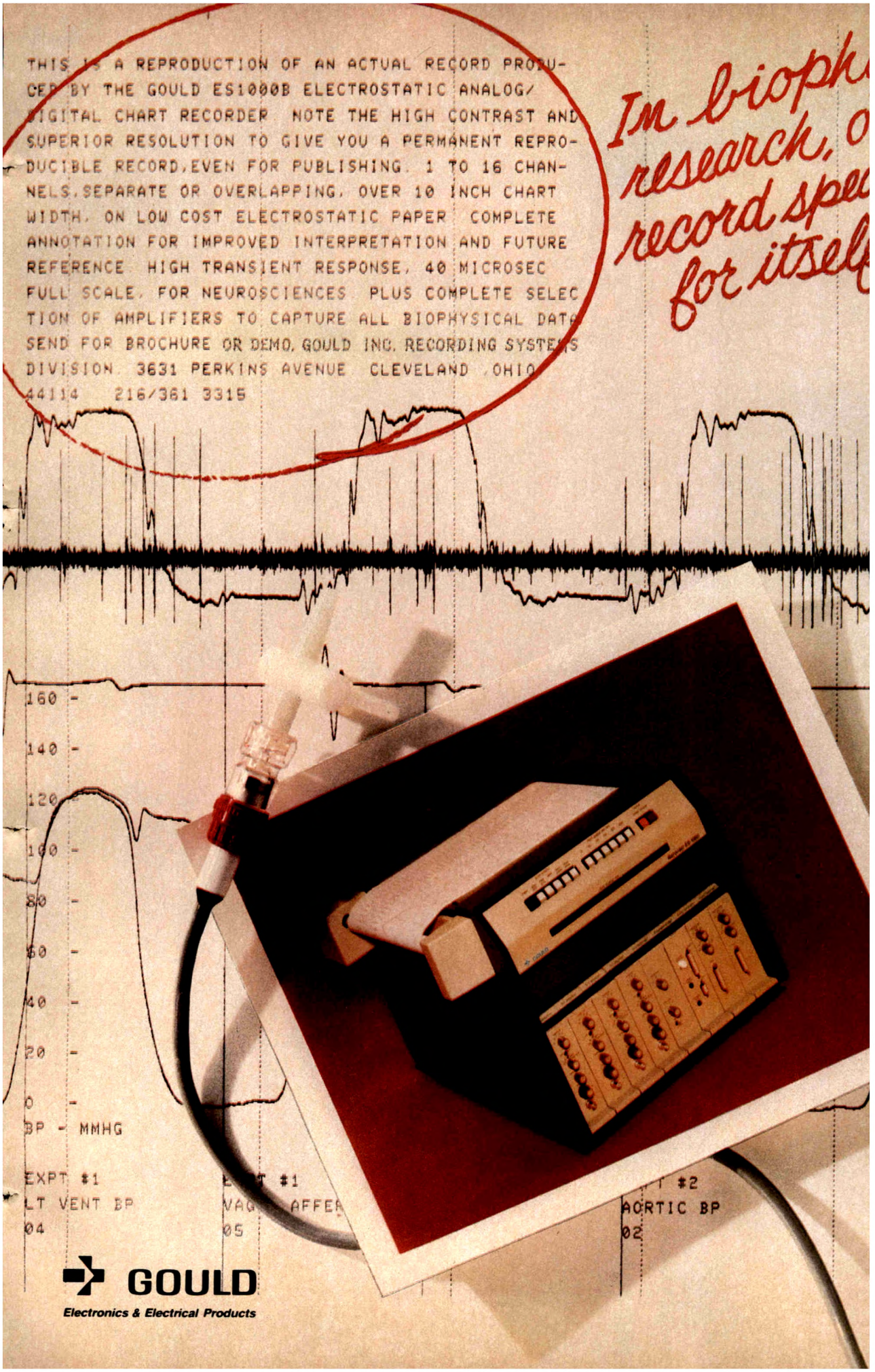
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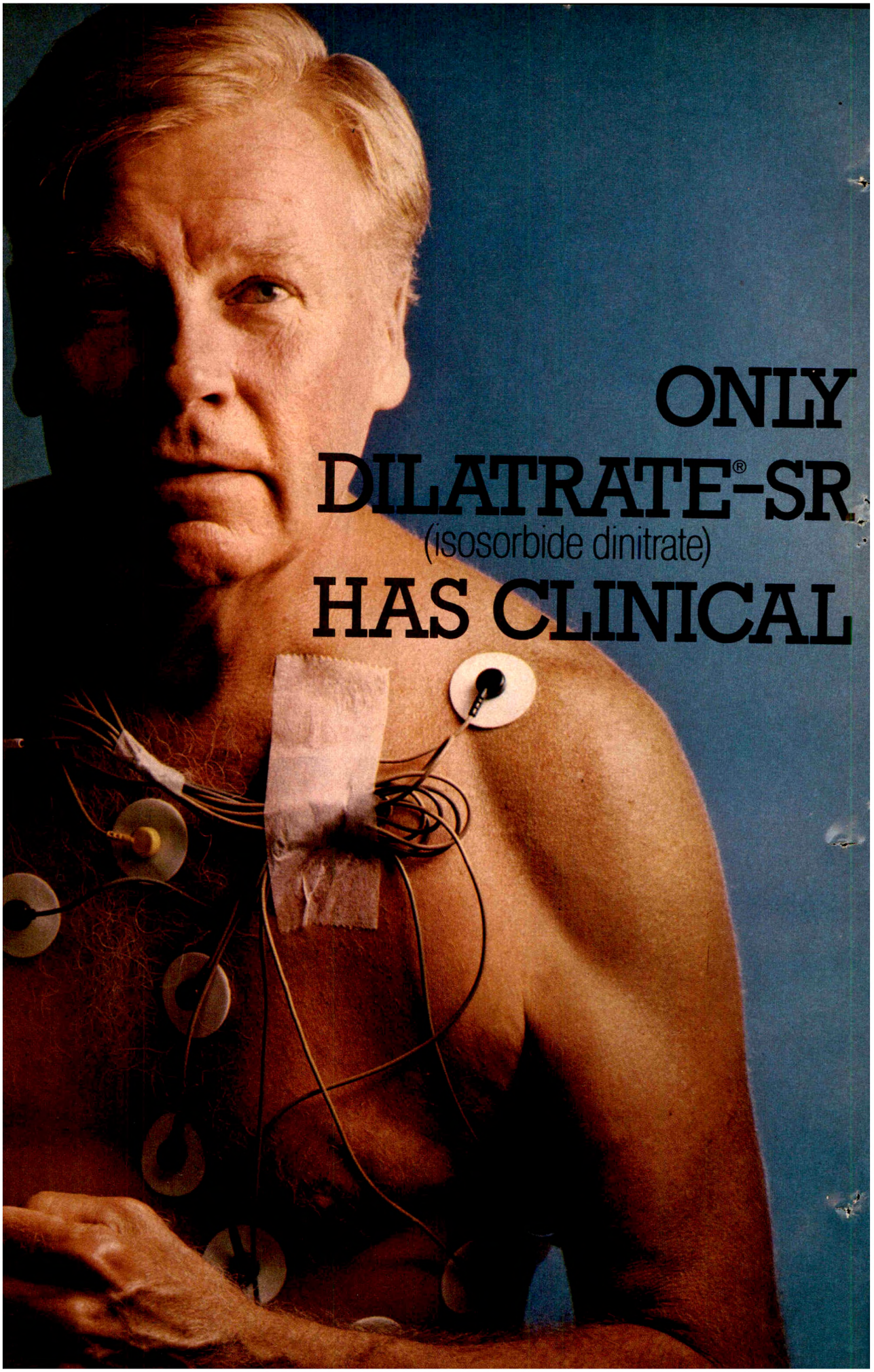
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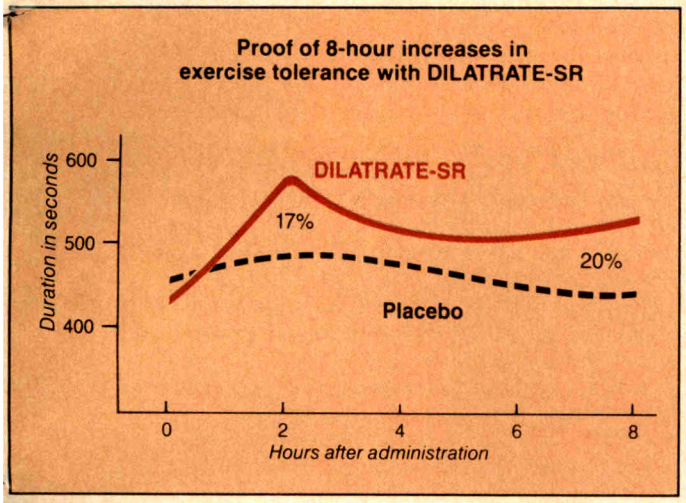
In treadmill tests, DILATRATE-SR produced a 17% increase in mean total exercise duration within 2 hours; after 8 hours the increase was 20%.



*Exercise duration and work capacity increased for a full 8 hours in angina patients**

In a double-blind, placebo-controlled study involving patients with chronic stable angina, significant improvement in exercise capacity was sustained for eight hours following administration of one 40 mg DILATRATE-SR capsule.[1]

This is the first study to demonstrate that a sustained-release nitrate formula can provide clinical effectiveness for a full eight hours. And, the advantage over placebo did not appear to be decreasing at the end of eight hours.

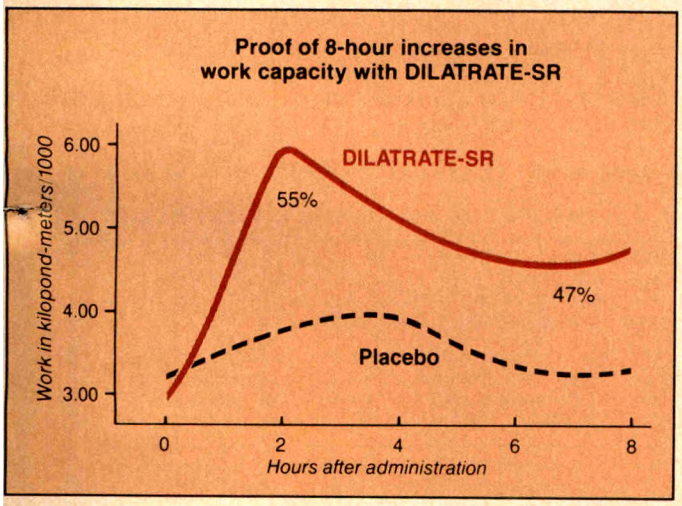
Increases in exercise tolerance translate into true patient benefits

Exercise tolerance tests provide objective measurements of improvement in work capacity that can be correlated with the anginal patient's daily activities. These results demonstrate that DILATRATE-SR can provide a positive impact on your patient's lifestyle.

Clinical support of plasma level studies

This clinical study supports previous blood assays which demonstrated that DILATRATE-SR provides significant plasma levels of ISDN for up to 12 hours.[2]

PROOF: 8-hour antianginal activity*



A 20% increase in duration of treadmill exercise means another minute or two at higher speed on a steeper incline. When mean work performance was calculated, DILATRATE-SR provided a 47% increase at 8 hours.

A unique method of delivering isosorbide dinitrate

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DILATRATE-SR simplifies antianginal therapy

The proven sustained activity of DILATRATE-SR offers anginal patients convenient b.i.d. dosage and can reduce the need for sublingual nitroglycerin.

*Please see brief summary of full prescribing information on following page. For full prescribing information, consult package insert.

References:

1. DiBianco R et al: Effects of a new oral slow release form of isosorbide dinitrate on the hemodynamics and exercise capacity of patients with angina — a placebo controlled and double blind study. *Circulation* (Supp II) 66:381, Oct 1982.
2. Dinsdale J, Allen J: Data on file, Medical Department, Reed & Carnrick.

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Reed & Carnrick / Piscataway, New Jersey 08854

Dilatrate®-SR
(isosorbide dinitrate) 40 mg

BRIEF SUMMARY

Indications: Based on a review of this drug by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: When taken by the oral route, is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATION: Idiosyncrasy to this drug.

WARNINGS: Data supporting the use of nitrates and nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

PRECAUTIONS: Tolerance to this drug, and cross-tolerance to other nitrates or nitrites may occur.

In patients with functional or organic gastrointestinal hypermotility or malabsorption syndrome it is suggested that either the 5 mg. or 10 mg. oral tablets or 2.5 mg. or 5 mg. sublingual tablets be the preferred therapy.

ADVERSE REACTIONS: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

For full prescribing information, consult package insert.

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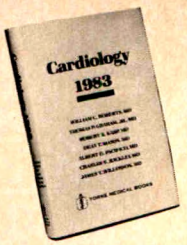
Cardiology 1983



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Ventricular Tachyarrhythmias in Prinzmetal's Variant Angina: Clinical Significance and Relation to the Degree and Time Course of S-T Segment Elevation

MARIO PREVITALI, MD, CATHERINE KLERSY, MD, JORGE A. SALERNO, MD, MARCELLO CHIMIENTI, MD, CLAUDIO PANCIROLI, MD, EGIDIO MARANGONI, MD, GIUSEPPE SPECCHIA, MD, MARIO COMOLLI, MD, and PIERO BOBBA, MD

Fifty-six patients with active Prinzmetal's variant angina were studied to determine the incidence and clinical significance of ventricular tachyarrhythmias and the correlation between arrhythmias and degree and time course of S-T segment changes during the ischemic attacks. Twenty-nine patients (Group I) had no ventricular arrhythmias in any of the 1,083 recorded episodes, while 27 patients (Group II) developed arrhythmias in 18% of the attacks. No significant differences in clinical, electrocardiographic, angiographic, or hemodynamic findings could be found between the 2 groups. In 23 of the 27 Group II patients, ventricular arrhythmias developed during maximal S-T segment elevation (occlusion arrhythmias), while in 10 they occurred during resolution of S-T segment changes (reperfusion arrhythmias); 6 of the latter patients also had occlusion arrhythmias. Eight of the 23 patients with occlusion arrhythmias and 6 of the 10 with reperfusion arrhythmias had ventricular fibrillation or ventricular tachycardia. Maximal S-T segment elevation was significantly greater ($p < 0.001$) in patients with occlusion arrhythmias than in those without arrhythmias. The episodes with reperfusion arrhythmias were significantly longer ($p < 0.001$) and showed a significantly greater S-T segment elevation ($p < 0.001$) than those without arrhythmias in Group I patients.

This study shows that significant ventricular tachyarrhythmias develop during ischemic attacks in about 50% of patients with active variant angina; clinical and angiographic features are not useful in distinguishing patients with arrhythmias from the others. Our findings suggest that in variant angina ventricular arrhythmias may be due to the effects of both coronary artery occlusion and reperfusion; both types of arrhythmias are correlated with the severity of ischemia, as measured by the degree of S-T segment elevation. Reperfusion arrhythmias also appear to be correlated with the duration of ischemia.

It is well known that ventricular tachyarrhythmias may be associated with ischemic attacks in patients with Prinzmetal's variant angina pectoris.[1–5] The spectrum of reported arrhythmias includes ventricular tachycardia,[1,4,5] ventricular fibrillation,[2,4,5] and ventricular premature complexes.[3–5] However, only few data are available on the incidence and clinical significance of ventricular tachyarrhythmias in large groups of patients with Prinzmetal's variant angina. Moreover, the mechanisms of ventricular arrhythmias associated with ischemic attacks in these patients are still under investigation. Experimental studies have shown that both occlusion of a major coronary vessel and reperfusion of the ischemic region may trigger ventricular tachyarrhythmias.[6–13] Since reversible coronary artery spasm leading to transient coronary occlusion and subsequent reperfusion is well established as the cause of variant angina pectoris, the same mechanisms demonstrated in experimental animals could play a role in the pathogenesis of ventricular arrhythmias in patients with variant angina. Although occlusion and reperfusion phases cannot be directly identified in man, experimental and clinical studies have shown that coronary artery occlusion is associated with S-T segment elevation[12,14,15] and reperfusion with a rapid return of the S-T segment to baseline.[12,16] Therefore, continuous

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TABLE I Clinical, Electrocardiographic, Angiographic, and Hemodynamic Findings in Group I Patients (Without Ventricular Tachyarrhythmias)

Case	Age (yr) & Sex	Previous Infarction	Site of S-T Segment Elevation	Coronary Arteriographic Data (% Stenosis)			EF (%)	LVEDP (mm Hg)
				RCA	LAD	LC		
1	47M		Inferior	50	50		60	20
2	37M		Anterior		75		56	15
3	51M		Anterior	100	90	90	50	16
4	69M		Anterior	...	...	...	...	...
5	66F		Anterior		90	75	45	19
6	59M		Inferior	90			72	10
7	45M		Inferior	50	50		...	...
8	59M		Anterior			90	63	...
9	46M		Anterior		75	75	53	9
10	66M		Inferior	50	...		57	...
11	53M	Inferior	Anterior	99	75		35	...
12	39M		Anterior		90		68	15
13	55M		Inferior	75			...	...
14	55M		Anterior	75	75		50	15
15	51M		Anterior	90	90	75	57	12
16	32M		Anterior	...	...	...	...	...
17	42F		Inferior	75			77	10
18	61M		Inferior	75			64	...
19	66M		Anterior	75	90		67	15
20	63M		Anterior		75	75	67	22
21	51M		Inferior	90			83	10
22	67M		Inferior	75			55	10
23	49M		Inferior	100	75		...	10
24	53F		Anterior		90		51	10
25	45M		Anterior	90	99		55	15
26	65M		Anterior	75	90	75	...	15
27	49M		Inferior	75			73	9
28	67M		Anterior	...	...	...	...	...
29	36M		Inferior	90		90	59	13

EF = ejection fraction; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; LVEDP = left ventricular end-diastolic pressure; RCA = right coronary artery.

TABLE II Clinical, Electrocardiographic, Angiographic, and Hemodynamic Findings in Group II Patients (With Ventricular Tachyarrhythmias)

Case	Age (yr) & Sex	Previous Infarction	Site of S-T Segment Elevation	Coronary Arteriographic Data (% Stenosis)			EF (%)	LVEDP (mm Hg)
				RCA	LAD	LC		
1	55M		Anterior	90	90		48	11
2	55F		Anterior		99		52	6
3	51M		Anterior	...	...		...	...
4	56M		Anterior	75	75	75	43	10
5	46M		Anterior		75		50	21
6	43M		Inferior	50			58	14
7	62M		Anterior	75	90	75	58	8
8	67M	Inferior	Anterior	75	75	75	57	20
9	51M	Anterior	Anterior		90		50	12
10	46M		Anterior		75		65	12
11	63M		Anterior	90	90		50	21
12	50M		Anterior		75		64	15
13	59M		Anterior Inferior	99	75	75	68	11
14	61M		Anterior		90		59	12
15	66M		Inferior	50	50		61	12
16	55M		Anterior	100	90	100	59	24
17	53M		Anterior		90		54	6
18	47M		Anterior		75		55	12
19	69M		Anterior	...	...		...	...
20	62M		Anterior Inferior	0	0	0	82	13
21	51M		Anterior	75	75	100	...	11
22	67M		Anterior			50	...	14
23	58M		Inferior	75			61	15
24	58M		Inferior	50	50		58	8
25	45M		Inferior	90		90	60	16
26	43M		Anterior	...	...	...	...	...
27	70M		Inferior	...	...	...	...	...

Abbreviations as in Table I.

monitoring of S-T segment changes during the attacks may be of value in identifying occlusion and reperfusion phases in patients with variant angina pectoris.

The present study was designed to evaluate the incidence of ventricular tachyarrhythmias and their correlation with clinical and angiographic findings in a large group of subjects with variant angina who underwent continuous electrocardiographic monitoring in coronary care unit. A further purpose of the study was to correlate ventricular tachyarrhythmias with the degree and time course of S-T segment elevation, in order to determine their relation with severity of ischemia and occlusion and reperfusion phases.

Methods

Patient selection: Fifty-six patients, 52 men and 4 women aged 32 to 72 years (mean 54 ± 9) who had frequent attacks of angina at rest associated with transient S-T segment elevation, were selected for the study. Nineteen of them also had effort angina. Three patients had a history of an old myocardial infarction; 2 of them showed transient ischemic electrocardiographic changes in a region different from the infarcted one and 1 in the same region. No patient had symptoms or clinical signs suggestive of heart failure. The basal electrocardiogram was normal in 16 patients, while 33 patients showed nonspecific S-T segment changes and/or flat or negative T waves in the leads showing S-T segment elevation during the attacks. Q waves indicative of a previous myocardial infarction were present in 3 patients, incomplete right bundle branch block in 2 patients, left anterior hemiblock in 4 patients, and left ventricular hypertrophy in 1 patient.

Continuous electrocardiographic recording: All patients were admitted to the coronary care unit for continuous electrocardiographic monitoring; 41 underwent continuous electrocardiographic recording at a paper speed of 2.5 mm/s on a 6-channel recorder (Hellige Multiscriptor 9400/6) using leads I, II, III, V_2, V_4, and V_6; whenever possible during ischemic attacks recordings were obtained at a paper speed of 10 or 25 mm/s for detailed analysis. Fifteen patients underwent Holter monitoring with use of a 24-hour tape recorder (Oxford Medilog Mark I 4-24). In all these patients continuous multichannel electrocardiographic recording was carried out before Holter monitoring in order to detect the leads showing the most prominent alterations during acute ischemia. After skin preparation pregelled disposable electrodes were applied and carefully taped to avoid motion artifacts. A bipolar lead system was used: In patients with anterior S-T segment elevation 2 precordial leads (modified V_2 and V_5) were recorded and in those with inferior ischemia a lead exploring diaphragmatic wall (modified III) and a precordial lead were used. Before each recording period a 1 mV calibration signal was recorded using a Medilog XC-2 calibrator. Before the tapes were analyzed, the gain control of the replay unit was adjusted so that the 1 mV calibration signal previously recorded produced a 10-mm deflection on the chart recorder of the analyzer. The tapes were played back at 60 times real-time on a replay unit (Oxford PB-2) into an electrocardiographic analyzer (Pathfinder Medical Reynolds) with an S-T segment plotter. The analog output of heart rate and S-T segment were fed into a linear recorder at a paper speed of 6 cm/h of real-time recording. Whenever S-T segment shift from baseline occurred, whether or not associated with chest pain, the electrocardiogram was recorded at 25 mm/s. Ventricular arrhythmias were detected automatically by the analyzer and in each case printed out on chart and validated by the investigator. In order to carefully evaluate the time relation between S-T segment changes and ventricular arrhythmias, a tapes were also printed on photographic paper by means c a fiber optic full disclosure system (Eliminator 7700 America Edwards).

The duration of continuous electrocardiographic moni toring ranged from 1 to 132 hours (mean 36). During the in vestigation no patient was treated with vasodilators, digitalis beta-blocking agents, or antiarrhythmic drugs; sublingua nitroglycerin was administered as needed.

S-T segment elevation of at least 1 mm from the baselin lasting at least 1 minute whether or not associated with ches pain was considered indicative of acute myocardial ischemia S-T segment elevation was measured in millimeters 80 m after the J point, taking the P-R segment as a reference in th lead showing the highest S-T segment elevation. Duration o the episodes was calculated from the first changes of S-T segment or T wave to return of S-T segment to baseline. Fo the purpose of this study, the following ventricular arrhyth mias were taken into consideration: (1) frequent (defined a ≥5 beats/min), paired or multiform premature ventricula beats; (2) ventricular bigeminy or trigeminy; (3) ventricula tachycardia, defined as ≥3 consecutive premature ventricula beats at a rate of ≥130 beats/min; and (4) ventricular fibril lation. Isolated premature ventricular beats occurring durin ischemia and those already present in basal recordings wer excluded from the analysis. Ventricular arrhythmias occurrin during the waxing phase or at the peak of S-T segment ele vation were considered related to the occlusion phase an those developing during or immediately after return of the S-T segment to baseline related to the reperfusion phase.

Angiographic study: Of the 56 patients, 49 underwen coronary angiography by the Sones technique and left ven triculography. Stenosis of >50% of the vessel diameter wa considered significant. Left ventricular angiography wa carried out in the 30° right anterior oblique projection and th ejection fraction was calculated according to the Dodg method.

Statistical analysis: Mean values of S-T segment elevatio and duration of ischemia for the episodes with and withou ventricular arrhythmias were determined in each patient. A unpaired t test was used to compare these parameters i Group I (without arrhythmias) and Group II (with arrhyth mias) patients and a paired t test for comparison of the epi sodes with and without arrhythmias in Group II patients Differences in the prevalence of clinical and angiographi characteristics in patients with and without arrhythmias wer compared using either a chi-square test or the unpaired t tes when appropriate. A probability (p) value <0.05 was consid ered statistically significant. Data are expressed as means ± standard deviation.

Results

On the basis of the presence of ventricular tachyar rhythmias during the attacks, patients were classifie in 2 groups: Group I was composed of 29 patients wh never showed ventricular arrhythmias during acut ischemia; Group II was composed of 27 patients i whom ventricular arrhythmias were recorded in ≥ ischemic episodes. Individual clinical and angiographi findings are summarized in Table I for Group I patient and in Table II for Group II patients.

Comparison of clinical findings between patient with and without arrhythmias: The clinical, elec trocardiographic, hemodynamic, and angiographi findings in Group I patients are compared with thos in Group II patients in Table III. The age distributio

TABLE III Clinical, Electrocardiographic, Angiographic, and Hemodynamic Findings in Group I (Without Ventricular Arrhythmias) and Group II (With Ventricular Arrhythmias) Patients

	Group I	Group II
Patients (n)	29	27
Sex	26M (90%)	26M (96%)
	3F (10%)	1F (4%)
Age (mean ± SD) (yr)	53 ± 10	56 ± 8
Previous infarction	1 (3%)	2 (7%)
Effort angina	10 (34%)	9 (33%)
Normal electrocardiogram	9 (31%)	7 (26%)
Site of S-T segment elevation		
Anterior	17 (59%)	19 (70%)
Inferior	12 (41%)	6 (22%)
Anterior & inferior	. . .	2 (7%)
Angiographic findings		
No lesions >50%	3/16 (11.5%)	5/23 (22%)
1 vessel disease	11/26 (42%)	9/23 (39%)
2 vessel disease	9/26 (35%)	4/23 (17%)
3 vessel disease	3/26 (11.5%)	5/23 (22%)
Ejection fraction (%) (mean ± SD)	59 ± 11	58 ± 9
LVEDP (mm Hg) (mean ± SD)	13 ± 4	13 ± 5

LVEDP = left ventricular end-diastolic pressure; SD = standard deviation.

and sex ratio were similar in the 2 groups. A history of previous infarction or effort angina and a normal electrocardiogram were found with similar frequency in the 2 groups. During the attacks S-T segment elevation in the anterior leads was more commonly documented in the patients with ventricular tachyarrhythmias, but the difference was not significant. No statistically significant differences were found in the extent of coronary lesions and basal left ventricular function between the 2 groups, although a greater proportion of patients with ventricular arrhythmias had normal or minimally diseased coronary arteries.

Relation between ventricular arrhythmias and time course and degree of S-T segment elevation: In Group I patients 1,083 ischemic attacks were recorded during 964 hours of continuous electrocardiographic monitoring (mean 33 ± 32); the mean duration of the attacks was 216 ± 189 seconds and the maximal S-T segment elevation during ischemia was 1.8 ± 1.0 mm.

Group II patients had 1,338 ischemic episodes during 1,039 hours of continuous electrocardiographic recording (mean 40 ± 29). Eighteen percent of the attacks were associated with arrhythmias. In 23 of these patients ventricular tachyarrhythmias developed close to or at the peak of S-T segment elevation (Fig. 1) and were considered occlusion arrhythmias, whereas in 10 patients arrhythmias appeared during or immediately after the return of the S-T segment to baseline (Fig. 2) and were classified as reperfusion arrhythmias; 6 of the latter patients also showed occlusion arrhythmias in the same or other ischemic attacks.

In the group with occlusion tachyarrhythmias 1 patient had ventricular fibrillation, 7 ventricular tachycardia, 8 ventricular bigeminy, 5 repetitive premature ventricular beats, and 2 frequent premature ventricular beats; the rate of ventricular tachycardia ranged from 132 to 280 beats/min (mean 190 ± 53). The mean duration of ischemic attacks was 494 ± 319 seconds; ventricular arrhythmias developed 180 ± 129 seconds after the beginning of ischemia. Maximal S-T segment elevation was significantly greater ($p < 0.001$) in the patients with occlusion ventricular arrhythmias than in Group I patients (Table IV). Eighteen of the 23 subjects with occlusion ventricular arrhythmias also had episodes without arrhythmias: the attacks associated with arrhythmias showed a significantly greater S-T segment elevation than did those without rhythm disturbances (6.3 ± 3.9 versus 3.5 ± 2.5 mm, $p < 0.001$).

In the group with reperfusion ventricular tachyarrhythmias, 1 patient developed ventricular fibrillation, 5 ventricular tachycardia, and 4 ventricular bigeminy. The rate of ventricular tachycardia ranged from 140 to 240 beats/min (mean 191 ± 56). Among the 6 patients

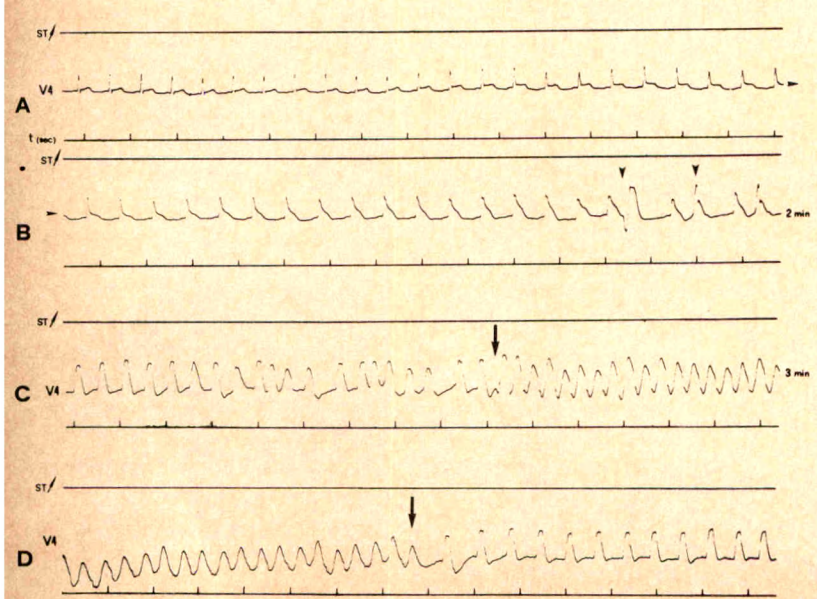

FIGURE 1. Occlusion ventricular arrhythmias in a patient with anterior S-T segment elevation. A bipolar lead similar to lead V_4 is monitored. At the onset of S-T segment elevation no ventricular arrhythmia is present (**strip A**). As the S-T segment elevation increases (**strip B; strips A and B** are continuous recordings), ventricular premature beats appear (**arrowheads**). After 2 minutes, at the time of maximal S-T segment elevation (**strip C**), ventricular tachycardia develops (**arrow**). When ventricular tachycardia reverts spontaneously to sinus rhythm (**strip D, arrow**), S-T segment elevation persists unchanged.

TABLE IV Comparison Between the Ischemic Episodes of Group I (Without Ventricular Tachyarrhythmias) and Group II (With Ventricular Tachyarrhythmias) Patients

	Group I	Group II	
		Occlusion VTA	Reperfusion VTA
Duration of ischemia (s)	216 ± 189	494 ± 319	801 ± 632*
Maximal S-T segment elevation (mm)	1.8 ± 1.0	5.2 ± 3.7*	6.3 ± 4.5*

* $p < 0.001$ compared with values in Group I.
All values are expressed as means ± standard deviation. VTA = ventricular tachyarrhythmias.

with ventricular arrhythmias during both occlusion and reperfusion phases, 3 showed ventricular tachycardia during both periods. The episodes associated with reperfusion arrhythmias in this group were significantly longer ($p < 0.001$) than those without arrhythmias in Group I patients (Table IV). In 6 of the 10 patients with reperfusion arrhythmias, the ischemic attacks lasted ≥10 minutes. Maximal S-T segment elevation was significantly greater ($p < 0.001$) in patients with reperfusion ventricular tachyarrhythmias than in Group I subjects (Table IV). In the 8 patients with reperfusion arrhythmias in whom ischemic episodes without rhythm disturbances were also present, the attacks associated with reperfusion arrhythmias showed a significantly longer duration (748 ± 568 versus 222 ± 109 seconds, $p < 0.05$) and a greater S-T segment elevation (7.1 ± 4.7 versus 3.5 ± 2.8 mm, difference not significant) than did those without arrhythmias.

Discussion

Incidence and clinical significance of ventricular arrhythmias in variant angina: The results of this study show that ventricular tachyarrhythmias are present in 1 or more ischemic attacks in 47% of patients with Prinzmetal's variant angina. Our findings are in agreement with those of Kerin et al,[5] who found sever dysrhythmias, including high-degree atrioventricula blocks, in 12 of 26 patients with variant angina, wherea other investigators[4] reported major rhythm distur bances, including severe bradyarrhythmias, in a smalle group of patients. The higher incidence of ventricula arrhythmias in our patients may be due to a differen patient population as well as to the fact that in the re ported study[4] the authors took into consideration onl patients with ventricular fibrillation or ventricula tachycardia; moreover, ventricular arrhythmias wer detected by central coronary care unit monitoring which consistently underestimates the frequency o ischemic attacks[17] and therefore, presumably, of ar rhythmias.

In the patients studied we did not find any significan correlation between the incidence of ventricular ar rhythmias and a series of clinical, electrocardiographic and angiographic parameters, including extent of cor onary artery lesions and baseline left ventricular func tion. Therefore clinical and angiographic features seen to be of limited value in recognizing patients with var iant angina who are at risk of developing life-threaten ing ventricular arrhythmias during the attacks. On th basis of our data, the severity of coronary artery diseas seems to play only a minor role in the pathogenesis o ventricular arrhythmias in variant angina, as previously suggested by other studies.[4,5] Recent experimenta findings[18] suggest that the risk of reperfusion ventric ular fibrillation may be greater in subjects without tha in those with coronary artery disease. In our study 3 o the 7 patients with reperfusion arrhythmias who un derwent coronary angiography showed normal or no critically diseased coronary arteries. Further studies i a larger population of patients with variant angina ar required to confirm the experimental results. Becaus in most of our patients left ventricular function wa normal or only mildly impaired, the influence of marked left ventricular depression on the frequency an severity of arrhythmias in variant angina is difficult t assess.

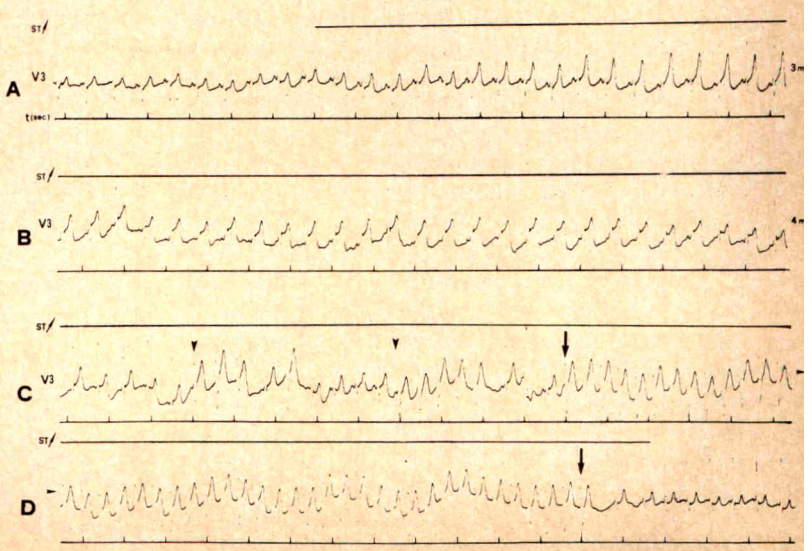

FIGURE 2. Reperfusion ventricular arrhythmias in a patient with anterior S-T segment elevation. A bipolar lead similar to lead V_3 is monitored. No ventricular arrhythmias occur at the onset of S-T segment elevation (**strip A**) and at the time of maximal S-T segment changes after 3 minutes of ischemia (**strip B**). When S-T segment elevation begins to decrease 4 minutes later (**strip C**), short runs of ventricular tachycardia (**arrowheads**) and then a sustained ventricular tachycardia (**arrow**) develop. Note that when the arrhythmia reverts spontaneously to sinus rhythm (**strip D, arrow**), the S-T segment has already returned to baseline.

Correlation of ventricular arrhythmias with severity of acute ischemia: In the present study as well as in previous reports,[5,19] the presence of ventricular arrhythmias during ischemic attacks was significantly correlated with the severity of ischemia, as estimated by the degree of S-T segment elevation: in fact, S-T segment elevation was significantly greater during the episodes associated with arrhythmias than during those without arrhythmias. Kerin et al[5] also showed that patients with ventricular arrhythmias during attacks of variant angina had S-T segment elevation of ≥4 mm, whereas in those without arrhythmias S-T segment elevation varied from 1.5 to 3 mm. Experimental studies suggest that, in the absence of intraventricular conduction disturbances, the degree of S-T segment elevation reflects the severity of ischemia[20]; moreover, S-T segment elevation correlates with the degree of tissue metabolic derangement,[21] reduction of coronary blood flow,[22] and alterations in intracellular potential.[23] Although experimental findings must be transferred cautiously to the clinical situation, the correlation between ventricular arrhythmias and degree of S-T segment elevation found in this study suggests that the severity of ischemia and its associated electrophysiologic alterations are critical in the genesis of ventricular arrhythmias in variant angina.

Relation of ventricular arrhythmias to occlusion and reperfusion phases: The experimental findings that both coronary artery occlusion and reperfusion are associated with malignant ventricular dysrhythmias, including ventricular fibrillation,[6–13] may be of clinical relevance, because in patients with variant angina coronary occlusive spasm and its subsequent release may reproduce the same sequence of events. The analysis of the relation of ventricular arrhythmias to the time course of S-T segment elevation in the patients studied showed that 23 of them had significant ventricular dysrhythmias close to or at the peak of S-T segment elevation, whereas in 10 patients ventricular arrhythmias occurred during resolution of the S-T segment alterations. Because there is experimental and clinical evidence that coronary artery occlusion is associated with S-T segment elevation[12,14,15] and reperfusion with return of S-T segment to baseline,[12,16] our findings suggest that in variant angina, ventricular arrhythmias may be triggered not only by coronary artery occlusion due to vasospasm, but also by reestablishment of coronary blood flow after relief of spasm.

In experimental animals the time course of ectopic activity is different after coronary artery occlusion compared with its release: Ventricular arrhythmias secondary to occlusion develop after a quiescent period of 1.5 to 2.5 minutes and reach a peak at 4 to 6 minutes[6,7,12]; by contrast, reperfusion dysrhythmias occur immediately after coronary artery release and are correlated with the duration of the antecedent period of coronary ligation.[9–12,24,25] The finding that in the patients studied occlusion arrhythmias developed at an average time of 3 minutes after the onset of ischemia is in keeping with the experimental results. Because the episodes associated with reperfusion arrhythmias were significantly longer than those without this type of arrhythmia, the duration of ischemia seems to be an important determining factor of reperfusion arrhythmias in human subjects also. Our results suggest that both occlusion and reperfusion arrhythmias are correlated with the degree of S-T segment elevation; thus the severity of myocardial ischemia seems to play a significant role in the pathogenesis of both types of dysrhythmia, although hemodynamic and nervous factors may significantly contribute to their development. Contrary to experimental studies showing a similar or even greater incidence of reperfusion arrhythmias than occlusion,[25,26] in the patients studied ventricular arrhythmias were more frequent during the occlusion phase than during reperfusion. This discrepancy could be due to the fact that in animals the incidence of reperfusion dysrhythmias increases as the period of preceding occlusion is prolonged from a few up to 30 minutes,[12,25] whereas the episodes of variant angina are usually of brief duration and so do not reproduce the metabolic and electrophysiologic alterations necessary for the development of arrhythmias during reperfusion.

Therapeutic implications: Patients with variant angina associated with severe ventricular arrhythmias have an early and late mortality higher than those without arrhythmias and are more likely to die suddenly.[4] Therefore they constitute a high-risk group in whom prevention of life-threatening arrhythmias is of utmost importance. In experimental studies various antiarrhythmic drugs used in the prevention of occlusion[27,28] or reperfusion[29–32] arrhythmias have led to equivocal and conflicting results. Because in variant angina coronary spasm is the underlying mechanism of acute ischemia leading to ventricular arrhythmias, a rational approach should aim at prevention of spasm rather than at treatment of arrhythmias once ischemia has developed. Calcium-antagonist drugs have been shown to be highly effective in the treatment of vasospastic angina[33–36]; moreover, experimental studies suggest that verapamil can prevent both occlusion and reperfusion ventricular tachyarrhythmias.[31,32,37] Therefore these drugs seem to be the treatment of choice in patients with vasospastic angina associated with ventricular tachyarrhythmias.

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Long-Term Responses to Nifedipine in Patients With Coronary Spasm Who Have an Initial Favorable Response

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Twenty-six patients with angina and coronary spasm participated in a randomized crossover trial comparing nifedipine with isosorbide dinitrate. Eighteen patients had a short-term beneficial response to nifedipine, and 14 of these were followed up for an average period of 9.4 months. During follow-up study, nifedipine was the primary therapy in these 14 patients, but other drugs were added when clinically necessary to control angina. There was an overall 86% beneficial response rate (>50% decrease in angina frequency). However, 2 patients had a large increase (>10 times) and 4 patients had a slight increase (transient) in angina frequency over the long term compared with the short-term response. The other 8 patients had a similar angina frequency compared with the short-term response. Of the 12 patients with a good response (transient slight increase or no change), 8 (67%) required additional drug therapy to maintain angina control. Nifedipine was discontinued in 2, and the dose was decreased in 3 of the 14 patients because of adverse effects. Three patients had a marked increase in angina at 9, 14, and 3 months, requiring hospitalization; 1 patient had coronary bypass for symptom control. Thus, patients with coronary spasm selected because of a favorable short-term response to nifedipine were effectively treated over the long term with nifedipine; however, additional therapy was often needed to control symptoms. Adverse effects were common, but simple reduction of nifedipine dose usually diminished the unwanted effects of the drug.

Patients with rest angina and coronary spasm often receive long- and short-acting nitrates, calcium antagonists, and various combinations of these medications. Short-term efficacy of calcium antagonists has been demonstrated.[1–3] Studies also suggest beneficial long-term results.[4–6] These results occur, however, in patients receiving nifedipine as additive therapy to other antianginal agents. Numerous questions remain to determine optimal long-term management of patients with coronary spasm. Does a beneficial short-term response predict the same long-term response? Does therapy with nifedipine prevent cardiac events? Is nifedipine useful as single or primary therapy for long-term angina prophylaxis in patients with coronary spasm? Are additional medications, surgical procedures, or both necessary to continue a good therapeutic response? In view of these questions, a prospective investigation was conducted to determine the long-term effects of nifedipine therapy in a group of patients with coronary spasm who had a good initial response to the drug.

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Methods

Patient selection: Twenty-six patients (22 men and 4 women) were entered into a double-blind randomized crossover trial comparing nifedipine and isosorbide dinitrate. All patients had angina, predominantly at rest, which was relieved by nitrates. All patients had cardiac catheterization studies performed before study entry. Our criteria for coronary spasm required demonstration of a major change in epicardial coronary diameter, either focal or diffuse, associated with objective evidence for transient myocardial ischemia reversed by nitrate.

All but 1 patient had angiographically documented coronary spasm. The latter patient had a normal coronary angiogram after sublingual nitrates were given. During angina, she had S-T elevation in electrocardiographic leads II, III, and aVF and varying degress of atrioventricular block, all of which were reversed by nitrates. No evidence of myocardial necrosis was found and left ventricular wall motion was normal.

TABLE I Long-Term Clinical Response

Patient	Nifedipine Dose (mg/day)	Duration of Therapy (mo)	Anginal Frequency: Long-Term Versus Previous Therapy	Anginal Frequency: Long-Term Versus Short-Term	Additional Antianginal Therapy
1	40	14	Increase	Increase	ISDN (40 mg)
2	80	8*	>50% decrease	NC	ISDN (80 mg), change to verapamil
3	40	19	>50% decrease	NC	NIF (40)
4	80	17	>50% decrease	NC	ISDN (40)
5	80†	9	NC	increase	Propranolol (360 mg), ISBN (120 mg), CABG
6	80†	3	>50% decrease	NC	. . .
7	40	16	ASX	NC	. . .
8	80†	7*	ASX	NC	ISDN (20 mg)
9	40	14	>50% decrease	NC	NIF (20 mg)
10	40	9	ASX	NC	. . .
11	80†	5	>50% decrease	Rare	. . .
12	120	5	>50% decrease	Rare	ISDN (40 mg)
13	80	3	>50% decrease	Rare	2% NTG ointment (4″)
14	120	3	>50% decrease	Rare	Topical NTG (10 mg), ISDN (120 mg)
Average	71	9.4	. . .	. . .	10 of 14

All patients had a >50% decrease in anginal frequency comparing short-term therapy and previous therapy.
* Drug discontinued because of adverse effects.
† Drug dose decreased by half because of adverse effects.
ASX = asymptomatic; CABG = coronary artery bypass graft; ISDN = isosorbide dinitrate; NC = no change; NIF = nifedipine; NTG = nitroglycerin.

These patients were entered into a short-term (12-week) trial which compared nifedipine with isosorbide dinitrate in a randomized double-blind crossover fashion. Details of this protocol and partial results of the short-term (12-week) trial have been reported previously.[1]

Of the 24 patients who completed the nifedipine phase of the random trial, 18 patients had a "beneficial" response defined as >50% decrease in angina frequency. Of these 18 patients, 14 continued to receive nifedipine and are the subjects of this report. The other 4 patients responded equally well to isosorbide dinitrate and continued to take the nitrate.

During follow-up study, the patients were evaluated by history, physical examination, electrocardiography, serum chemistry tests, and complete blood count, carried out at least every 2 months. Angina frequency and nitroglycerin consumption were tabulated from review of daily diaries.

Analysis of results: The lead-in phase of the short-term double-blind protocol was considered the baseline period for prior antianginal therapy and was used for all subsequent comparisons. The nifedipine phase of the short-term double-blind protocol was used to assess short-term responses. A >50% change in angina frequency was considered a beneficial response. The long-term responses were averaged monthly over the entire duration of follow-up study for each patient and compared with baseline and short-term response to nifedipine.

Results

Clinical data are summarized in Table I. The average length of follow-up study for the 14 patients was 9.4 months (range 3 to 19). All patients took nifedipine alone during the short-term portion of the study. Four patients (Patients 5, 6, 8, and 11) required a dose decrease from 80 to 40 mg/day because of adverse effects (fatigue in 1, edema in 1, headache in 1, and dizziness in 1). In 2 of these 4 patients (Patients 5 and 8), additional therapy was necessary to control angina. One of these 2 patients (Patient 8) eventually had the nifedipine discontinued because of adverse effects. One patient was asymptomatic with short-term therapy (Patient 11) but with dose reduction had rare (<1/week) angina; no additional therapy was instituted. The fourth patient (Patient 6) was poorly compliant and was changed to long-acting nitrates after 3 months. He was subsequently lost to follow-up study.

Two additional patients (Patients 4 and 10) had adverse effects during short-term treatment which resolved as therapy continued. In 1 of the remaining patients (Patient 2), nifedipine was discontinued because of adverse effects. This patient was given verapamil and responded satisfactorily. No other patient had a new adverse effect during long-term therapy.

No patients had abnormalities of serum chemistry values or complete blood count over the follow-up period.

Comparison of long-term therapy with previous antianginal therapy: Of the 14 patients, only 1 (Patient 1) had increased angina compared with previous therapy, which consisted of only sublingual nitrates. One other patient (Patient 5) had no change in angina frequency. Of the remaining 12 patients, 9 had a >50% decrease in anginal frequency and the other 3 were asymptomatic. This represents an 86% beneficial response with nifedipine compared with medication given before study.

Comparison of long-term with short-term therapy: Two patients (Patients 1 and 5) had a major increase (>10 times) in frequency of angina with long-term therapy. Four other patients (Patients 11, 12, 13 and 14) had a slight increase in symptoms compared with short-term results, but their angina frequency was <1/week and was considered a satisfactory response

Three patients (Patients 7, 8, and 10) remained asymptomatic with long-term therapy and the remaining 5 patients continued with a response similar to their short-term response.

Additional antianginal therapy: The 2 patients who had increased anginal frequency required additional therapy; 1 had long-acting nitrates (Patient 1), and the other had long-acting nitrates, propranolol, and finally coronary artery bypass surgery (Patient 5). Despite this additional treatment, both patients remained symptomatic. Six other patients (Patients 2, 4, 8, 12, 13, and 14) required long-acting nitrates to maintain a good therapeutic response. Two patients (Patients 3 and 9) had nifedipine increased by 40 and 20 mg day, respectively. Of the 12 patients who had a satisfactory beneficial long-term response, 8 (67%) required therapy in addition to their initial nifedipine dose to control angina.

Cardiac events: Cardiac events were defined as unstable angina, myocardial infarction, and sudden death. Only 3 patients (Patients 5, 9, and 14) had cardiac events while receiving long-term therapy. One patient of these 3 (Patient 14) had recurrent rest angina requiring hospitalization shortly after the short-term therapy trial. With addition of long-acting nitrates, her symptoms have been well controlled. Another patient (Patient 9) also had recurrent rest angina requiring hospitalization approximately 1 year after therapy was begun. The third patient (Patient 5) had rapidly increasing angina and underwent coronary artery bypass surgery. He had a perioperative myocardial infarction. It is not known whether coronary spasm was responsible for the myocardial infarction but subsequent catheterization revealed closure of all bypass grafts. No other patient experienced rest angina requiring hospitalization, myocardial infarction, or sudden death during the long-term follow-up period.

Discussion

In a group of patients with rest angina due to coronary spasm who had a good short-term response to nifedipine, the drug was effective in decreasing angina frequency in many over an average 9 month follow-up period. Eight of these 12 patients, however, required either a dose increase or additional antianginal therapy to maintain the good short-term response. Adverse effects necessitated discontinuation of therapy in 2 patients and decreasing the dose in 3 (total 36%). Coronary events (unstable angina requiring hospitalization) occurred in 3 patients.

Limitations: This study reports the long-term clinical responses of a group with an initial favorable response to nifedipine. There are several limitations in this study. First, there were no controls. Second, there was no uniform attempt to wean therapy or rechallenge with provocative agents such as ergonovine. Evaluation of spontaneous remission is thus impossible in all patients. A third limitation is the method used to average episodes of chest pain. Anginal frequency is variable in this group of patients. We arbitrarily averaged the number of episodes of pain per month for each patient over the follow-up period. Other methods may be used. Finally, there were no ambulatory electrocardiographic recordings made in the follow-up period. Our data, therefore, only represent symptomatic myocardial ischemia and are probably not a measure of total episodes of transient ischemia.

An additional problem that warrants consideration when evaluating long-term therapy of patients with coronary artery spasm is the spontaneous variability of symptoms.[7,8] Spontaneous attenuation of symptoms has been reported as high as 38%.[7] This is similar to the number in the present patient population who have remained in good clinical control with nifedipine alone. Seven of these patients have had their drug discontinued for various reasons. Only 1 has remained asymptomatic. Thus, it is not known whether current nifedipine therapy is needed to control symptoms.

Do short-term responses predict long-term responses? Only 2 patients had a major increase in anginal frequency comparing long- and short-term responses. Four other patients had a slight increase in symptoms which were controlled with long-acting nitrates or no additional therapy. These data are similar to other reports of the long-term efficacy of nifedipine.[4,5] Results from this study suggest that if patients demonstrate a good initial response, maintenance of decreased anginal frequency is possible in most patients but not necessarily with nifedipine alone.

Does nifedipine prevent cardiac events? Various investigators have reported a grave prognosis in patients with angina secondary to coronary spasm. MacAlpin et al[9] reported a 15% incidence of sudden death and 25% incidence of myocardial infarction within the first 3 months of symptoms. Recently, Miller et al[10] reported 114 patients with coronary spasm. They noted a 17% incidence of sudden death; no differences were found with respect to coronary artery disease or ventricular dysfunction. Recent data from Gerstenblith et al[11] in a group of patients with rest pain accompanied by electrocardiographic changes suggest nifedipine protects against some cardiac events, especially in those patients with S-T elevation. The current study group perhaps represents a low-risk group of patients for coronary events since anginal patterns were stable and angina was present, in many cases, for a prolonged period of time. Despite this, there was still a 21% incidence of cardiac events. Nifedipine does not seem to prevent their occurrence.

Nifedipine as primary therapy versus additional antianginal therapy: Although 12 patients had a good therapeutic response, 8 (67%) required additional antianginal therapy to maintain this response. The therapy of patients reported in this study differs from those previously reported in that nifedipine was the primary treatment. It was used as additive therapy in other trials.[4–6]

The patients in this report represent those who responded favorably to initial therapy with nifedipine alone. One might expect that long-term response to therapy would be favorable as these patients represent a select group. Despite this selection bias, 67% required

additional therapy to maintain good clinical response.

Adverse effects of the drug did limit long-term therapy in many patients (5 of 14) who responded satisfactorily during initial therapy. We have found a slightly higher incidence of adverse effects than that previously reported.[2,4–6] The explanation for this is unclear. Two patients with adverse effects responded well to a lower dose of nifedipine and a low dose of a long-acting nitrate. Combination therapy (nifedipine and nitrates) appears to be well tolerated by most patients.

All available published data suggest that nifedipine is effective therapy for angina in patients with coronary spasm. The current study confirms these results in a group of patients selected from a random trial who responded favorably to nifedipine and who were followed for approximately 1 year. However, adverse effects are relatively common and additional medications are often necessary to maintain a beneficial clinical response. Thus, it seems likely that individual drug dose adjustment and combination of nifedipine with other drugs known to be efficacious in patients with coronary artery spasm may be the logical and most effective way to treat patients with this condition.

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Prognostic Value of Resting and Submaximal Exercise Radionuclide Ventriculography After Acute Myocardial Infarction in High-Risk Patients With Single and Multivessel Disease

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In patients who survive the acute phase of myocardial infarction, those with multivessel coronary artery disease generally have a worse prognosis than those with single-vessel disease. However, some patients with significant multivessel stenoses have a good prognosis, whereas some with a significant single-vessel stenosis have a poor prognosis. Thus, although definition of coronary anatomy may be helpful, it is a not a fail-safe prognosticator. In this retrospective analysis, the association of abnormalities at rest and during submaximal exercise testing with radionuclide ventriculography after acute myocardial infarction with major cardiac complications (death, recurrent infarction, severe angina or congestive heart failure) in the ensuing 6 months was assessed in patients with single and multivessel disease. Coronary angiography and submaximal exercise testing with radionuclide ventriculography were performed within 3 months of each other in 42 patients. Eleven of the 16 patients with single-vessel coronary stenosis had major cardiac complications. The subsequent course of these 16 patients was correctly predicted by left ventricular ejection fraction (LVEF) ≤0.40 in 8 patients, by LVEF <0.55 in 7 patients, by failure of LVEF to increase by 0.05 units in 13 patients, and by an increase in left ventricular end-systolic volume index (LVESVI) during exercise >5% above baseline in 11 patients. Of the 26 patients with multivessel coronary artery disease, 24 had major cardiac complications. The subsequent course of these 26 patients was correctly predicted in 13 by LVEF ≤0.40, in 20 by LVEF <0.55, in 25 by a failure of LVEF to increase by 0.05 units during exercise, and in 20 by an increase in LVESVI by >5% during exercise. Thus, submaximal exercise testing with radionuclide ventriculography may provide valuable prognostic information concerning the occurrence of major cardiac events after myocardial infarction not only in patients with multivessel disease, but also in those with single-vessel disease. Exercise-induced abnormalities of left ventricular function may have greater prognostic importance than the delineation of coronary arterial anatomy or the assessment of residual left ventricular function at rest.

After the acute phase of myocardial infarction (MI), certain patients remain at risk of developing serious late complications. Recent attempts to identify those patients at risk of late complications have utilized a variety of techniques: Some attempt to quantitate the amount of irreversibly damaged myocardium (for example, serial creatine kinase determinations and imaging with technetium stannous pyrophosphate or thallium), whereas others assess residual myocardial function (radionuclide ventriculography or echocardiography).[1–13] Still other techniques attempt to assess the amount of viable myocardium at risk of further damage. Specifically, submaximal exercise testing has been reported to be useful in the detection of patients at risk of developing further complications after infarction, and the simultaneous use of radionuclide techniques seems to improve both the sensitivity and specificity of exercise testing in detecting high-risk patients.[14–22] Alternatively, coronary angiography allows the recognition of patients with significant single or multivessel coronary arterial stenoses after MI; the presence of single-vessel disease is generally associated with a better

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prognosis[23–26] because those with multivessel disease presumably have a greater amount of myocardium at risk of further damage. This retrospective analysis assesses the value of radionuclide ventriculography at rest and during submaximal exercise testing as predictors of major cardiac complications in patients with single or multivessel coronary artery disease.

Methods

Patient group: All patients admitted to the Coronary Care Unit at Parkland Memorial Hospital, Dallas, Texas with MI between August 1978 and August 1981 were considered for the present study. However, only those who underwent both submaximal exercise testing with radionuclide ventriculography and coronary angiography within 3 months of each other were included in this study. Submaximal exercise testing with radionuclide ventriculography was performed before hospital discharge in most patients after MI except for those with persistent angina at rest, severe congestive heart failure, or musculoskeletal disorders which would limit exercise, and those who would not consent to the procedure. Coronary angiography was performed only in certain clinical settings, namely, recurrent typical and atypical chest pain after MI in the hospital in 29 patients, infarct extension in 5 patients, congestive heart failure in 3 patients, a markedly abnormal exercise test at low work loads in 2 patients, refractory high-grade ventricular ectopy in 1 patient, and relatively young age (<40 years) in 2 patients. Twenty-one patients underwent catheterization during their initial admission for MI and 21 were readmitted subsequently for catheterization. Thus, the patients were a high-risk subgroup with a high incidence of early post-MI morbidity, and represent approximately 10 to 20% of the total number of patients with MI seen during this time period at Parkland Memorial Hospital.

The study group comprised 31 men and 11 women, aged 25 to 70 years (mean 50 ± 11). The diagnosis of MI was based on the presence of electrocardiographic, enzymatic (creatine kinase and creatine kinase-B isoenzymes), and scintigraphic (technetium-99m pyrophosphate) criteria.[27,28] MI was designated "transmural" when there were new Q waves ≥0.04 second in duration with associated ST-T wave changes, or a loss of R-wave height ≥50% in 2 or more leads of a conventional 12-lead electrocardiogram. The presence of typical ST-T wave changes and/or a loss of R-wave height <50% with associated enzymatic and scintigraphic changes compatible with MI was designated a "nontransmural" infarction.[29,30] The location of a transmural infarction was defined as either anterior (by the presence of typical changes in leads I, aVL, or V_1 to V_6) or inferior (by changes in leads II, III, or aVF).

Exercise testing protocol: All patients underwent supine bicycle exercise testing with radionuclide ventriculography 19 ± 9 (standard deviation) (range 12 to 52) days after infarction while taking their usual medications. The Frank lead system was used for continuous monitoring of the electrocardiographic response to exercise.[31] Cuff-determined blood pressures were also recorded at rest and near the completion of each work load. Exercise commenced at 150 or 300 kilopond-meters (kpm)/min and increased by 150 to 300 kpm/min at each subsequent exercise level depending on age, physical condition, and performance at the previous work load. The patients exercised for 4 minutes at incremental work loads until 1 of the following endpoints was reached: (1) a heart rate of 130 beats/min; (2) complex ventricular arrhythmias; (3) progressive chest discomfort compatible with angina pectoris; (4) S-T segment depression ≥0.2 mV (0.08 second after the J point) compared with the resting electrocardiogram; (5) a decrease in blood pressure during exercise; (6) exhaustion or marked dyspnea. Electrocardiographic monitoring was continued for 10 minutes after the completion of exercise.[32,33]

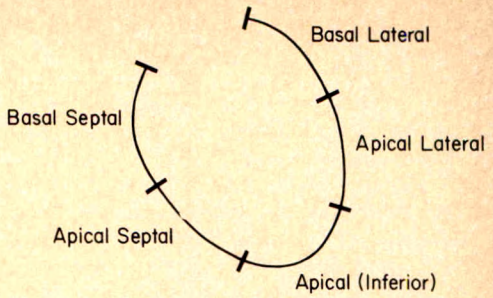

FIGURE 1. Wall segment identification and analysis. The left ventricl was divided into 5 segments of approximately equal length. Segmenta wall motion abnormalities before and during exercise were graded a follows: 4 = normokinesia; 3 = mild hypokinesia; 2 = severe hypok nesia; 1 = akinesia; and 0 = dyskinesia.

Radionuclide ventriculography: Multigated equilibriur blood pool imaging was performed using an in vivo techniqu of labeling red blood cells with 20 to 30 mCi of technetium 99m sodium pertechnetate.[20] Images were acquired using parallel-hole collimator and a gamma scintillation camer (Technicare Series 120, Solon, Ohio). Data acquisition wa performed in a modified 15° to 60° left anterior oblique pro jection with a 0° to 20° caudal tilt adjusted to provide the bes definition of the interventricular septum. All images wer acquired at a temporal resolution of 32 frames per cardia cycle for a preselected time interval of 3 minutes. Data ac quisition was commenced at each work load after 1 minute c exercise.[14] Left ventricular ejection fraction (LVEF) wa calculated using a standard count-related technique, afte background subtraction.[34] Left ventricular volumes wer calculated using a nongeometric technique recently describe from our laboratory.[34,35] Left ventricular segmental wal motion was analyzed subjectively from a cinematic display b 2 experienced observers. The left ventricle was divided int 5 segments as shown in Figure 1. Each segment was grade according to the following scale: 0 = dyskinesia, 1 = akinesia 2 = severe hypokinesia, 3 = mild hypokinesia, and 4 = nor mokinesia. The scores for all segments were summed both a rest and at each exercise level and expressed as a percentag of the maximal possible score. New wall motion abnormalitie during exercise were categorized according to their locatio as occurring in a previously abnormal area or in an adjacen or remote area by comparison with the ventriculogram at res Two levels of abnormal left ventricular function at rest wer defined, namely, LVEF ≤0.40 and <0.55, respectively. A abnormal response to exercise was defined as a failure t achieve an increase in LVEF of 0.05 units, or an increase c end-systolic volume index (LVESVI) by ≥5%.

Coronary angiography: All patients underwent left-side cardiac catheterization and coronary angiography in multipl projections 36 ± 23 days after their MI. The coronary angio grams were interpreted by at least 2 experienced observer who had no knowledge of the clinical course or the result c the exercise test with radionuclide ventriculography. A lesio was designated as significant when it involved ≥70% of th luminal diameter of the vessel.

Follow-up: Each patient was followed up closely in th cardiology clinic for 8 ± 6 months. Patients were classified int 2 groups based on the presence or absence of "major cardia complications" during the period of follow-up, including: (1 sudden death; (2) death due to cardiac causes; (3) recurren

MI; (4) class III or IV angina pectoris; and (5) congestive heart failure resistant to therapy. The remaining patients were either asymptomatic or had mild angina or congestive heart failure that responded to medical therapy.

Statistical analysis: The patients described in this study represent a high-risk subgroup of patients who underwent submaximal exercise testing with radionuclide ventriculography and coronary angiography after acute MI and who had a higher incidence of late complications than would be anticipated in an unselected group after MI. Therefore, we have stated our findings in specific rather than general terms and have reported the frequency with which each of the radionuclide-determined variables predicted the correct outcome in our group of patients with single and multivessel coronary artery disease.

Data are expressed as mean ± 1 standard deviation. Comparison of proportions in 2 groups was performed using an adjusted chi-square analysis.[36] A comparison of means was performed, where appropriate, using Student's *t* test modified for unequal variances.[36] A 2-tailed p value ≤0.05 was considered significant.

Results

Clinical features: The age and sex of the patients, as well as the site and extent of infarction, the presence or absence of a previously documented infarction, or systemic arterial hypertension are listed in Table I. Patients with significant single-vessel coronary arterial stenoses tended to have a lower incidence of previous MI, but this difference was not statistically significant (p = 0.09).

Coronary angiography: Sixteen patients had angiographic evidence of single-vessel coronary arterial stenosis, whereas 26 had significant double- or triple-vessel disease. The vessels involved, as well as the site of the infarction, are listed in Tables II and III. Vessels with noncritical narrowings are also listed in these tables.

Rest and exercise radionuclide ventriculography: The results of the rest and exercise radionuclide ventriculographic studies for individual patients are shown in Tables I to III and in Figures 2 and 3. Only 3 patients with single-vessel disease had LVEF ≤0.40, compared with 13 of 26 with multivessel disease (p = 0.09). The mean LVEFs in patients with single and multivessel disease were 0.55 ± 0.17 and 0.44 ± 0.14, respectively (p <0.03). The LVEF response to exercise was more normal in patients with single-vessel disease (+0.02 ± 0.10 versus −0.06 ± 0.06, p <0.01) (Table I). LVESVI at rest was smaller in patients with single-vessel disease than in those with multivessel disease (42 ± 25 versus 63 ± 28 ml/m^2, p <0.02) and the mean increase in LVESVI during exercise in patients with single-vessel disease was smaller than in those with multivessel disease (+2 ± 9 versus +12 ± 15 ml/m^2, p = 0.01).

Follow-up and prognostic value of rest and exercise radionuclide ventriculography in relation to coronary anatomy: The results of clinical follow-up in each patient are listed in Tables II and III. Most of the patients with 2- or 3-vessel disease had a complicated course after infarction, whereas patients with single-vessel disease had a variable course.

In the 16 patients with single-vessel coronary artery disease, the subsequent course was correctly predicted in 13 by LVEF response to exercise, in 8 by resting LVEF ≤0.40, and in 7 by resting LVEF <0.55 (p = 0.07

TABLE I Clinical Characteristics and Results of Exercise Radionuclide Ventriculography in Patients With Single and Multivessel Coronary Artery Disease

	Single-Vessel Disease	Multivessel Disease	p Value
Cases (n)	16	26	
Age	48 ± 11	51 ± 12	NS
Male	13	18	NS
Female	3	8	NS
Hypertension	4	5	NS
Previous MI	1	9	NS
Trans anterior	6	10	NS
Trans inferior	6	7	NS
Nontrans	4	9	NS
Work load achieved (kpm/min)	347 ± 195	259 ± 150	NS
Maximal heart rate (beats/min)	115 ± 17	112 ± 18	NS
Chest pain on exercise (patients)	3	8	NS
S-T segment depression (patients)	2	11	NS
S-T segment elevation (patients)	2	4	NS
Resting LVEF	0.55 ± 0.17	0.44 ± 0.14	p <0.03
Resting LVEDVI (ml/m^2)	79 ± 22	107 ± 39	p <0.005*
Resting LVESVI (ml/m^2)	42 ± 25	63 ± 28	p <0.02
Resting WMS (% of normal)	82 ± 21	71 ± 19	NS
ΔEF	+0.02 ± 0.10	−0.06 ± 0.06	p <0.01*
ΔLVESVI (ml/m^2)	+2 ± 9	+12 ± 15	p = 0.01*
ΔWMS (%)	−6 ± 13	−8 ± 8	NS
Remote or adjacent WM abnormality	3	9	NS
WM abnormality in the same area involved at rest	13	17	NS

* Welch approximation of the *t* test.

LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; Nontrans = nontransmural infarction; NS = not significant; Trans = transmural infarction; WM = wall motion; WMS = wall motion score; Δ = change.

TABLE II Patients With Single-Vessel Disease: Anatomic Findings, Response to Submaximal Exercise and Follow-Up

Case	Infarct	Coronary Artery (% Decrease in Diameter)							Resting LVEF	ΔLVEF	Resting ESVI (ml/m²)	ΔESVI (ml/m²)	Angina During Exercise	S-T Change (mm) on ECG	Follow-Up					
		LM	LAD	LD	LC	LOM	R	PD							Death	MI	UA	LA	CHF	CABG
1	Ant T	...	75	...	...	...	...	...	0.63	+0.11	33	−3	0	0	0	0	0	0	0	0
2	Ant T	...	100	...	...	...	50	...	0.63	−0.03	29	+6	0	0	+	+	0	0	0	0
3	Ant T	...	90	50	25	...	25	...	0.13	+0.01	108	+6	0	↓1	0	0	0	+	+	0
4	Ant T	...	95	...	...	...	...	...	0.58	−0.10	32	+12	0	0	0	0	+	0	0	0
5	Inf T	...	...	...	...	...	99	...	0.46	+0.06	65	−2	0	0	0	0	0	0	0	0
6	Inf T	...	...	...	50	...	100	...	0.60	+0.08	31	−2	0	↓2	0	0	0	0	0	0
7	Inf T	...	...	...	...	...	75	...	0.70	+0.15	22	−8	0	↑1	0	0	+	0	0	0
8	Inf T	...	...	...	...	...	100	...	0.55	+0.17	48	−19	0	0	0	0	0	+	0	+
9	NT	...	99	...	50	...	25	...	0.70	−0.02	18	+2	+	0	0	0	0	+	0	0
10	NT	...	90	...	...	...	...	...	0.70	+0.14	16	−5	0	0	0	0	0	+	0	+
11	Ant T	...	100	100	...	...	50	...	0.21	+0.03	70	−2	+	0	0	0	+	0	0	+
12	Ant T	...	99	...	50	...	...	...	0.56	−0.06	61	+5	+	0	0	0	0	0	0	0
13	NT	...	90	...	...	...	...	...	0.65	−0.16	29	+16	0	0	0	0	0	0	0	0
14	NT	...	90	50	...	...	50	...	0.69	−0.08	23	+4	0	0	+	0	+	0	0	0
15	Inf T	...	...	...	...	...	100	...	0.37	−0.03	53	+2	0	↑1	0	0	+	0	0	0
16	Inf T	...	...	...	...	...	100	...	0.59	+0.01	26	+12	0	0	0	0	+	0	0	0

Coronary arterial stenoses are expressed as the percentage of luminal diameter narrowing.
+ = present; 0 = absent; Ant T = anterior transmural; CABG = coronary artery bypass graft; CHF = congestive heart failure; ESVI = end-systolic volume index; ΔESVI = change in ESVI with exercise; Inf T = inferior transmural; LA = limiting angina; LAD = left anterior descending coronary artery; LC = circumflex coronary artery; LD = diagonal branch; LM = left main coronary artery; LOM = circumflex marginal branch; LVEF = left ventricular ejection fraction; ΔLVEF = change in LVEF with exercise; MI = myocardial infarction; NT = non-transmural; PD = posterior descending artery; R = right coronary artery; UA = unstable angina.

TABLE III Patients With 2- or 3-Vessel Disease: Anatomic Findings, Response to Submaximal Exercise and Follow-Up

Case	Infarct	Coronary Artery (% Decrease in Diameter)							Resting LVEF	ΔLVEF	Resting ESVI (ml/m²)	ΔESVI (ml/m²)	Angina During Exercise	S-T Change (mm) on ECG	Follow-Up					
		LM	LAD	LD	LC	LOM	R	PD							Death	MI	UA	LA	CHF	CABG
17	Ant T	...	95	...	...	...	...	90	0.59	−0.07	52	+9	0	0	+	0	0	+	0	0
18	Ant T	...	95	...	100	...	95	...	0.42	−0.13	96	+66	0	↓2	0	0	0	+	0	+
19	Ant T	...	90	100	100	...	90	100	0.30	−0.05	126	+7	+	0	0	0	0	+	0	+
20	Ant T	...	75	...	...	...	100	...	0.31	−0.01	64	+3	0	0	0	0	0	+	0	+
21	Ant T	...	50	80	90	...	100	...	0.68	−0.17	17	+9	+	↑1	0	0	0	+	0	0
22	Ant T	...	100	...	90	75	...	...	0.40	−0.12	66	+18	+	↓2	0	0	0	+	0	+
23	Inf T	...	50	60	95	...	100	...	0.37	−0.12	115	+46	+	0	0	0	0	+	0	0
24	Inf T	...	100	...	...	65	90	...	0.39	−0.04	94	+15	+	0	0	+	+	0	0	0
25	NT	...	40	95	...	80	...	90	0.80	−0.07	31	−4	0	↓2	0	0	0	+	0	+
26	Ant T	...	100	...	...	90	99	...	0.21	−0.07	83	+12	0	↑1	+	0	0	0	0	0
27	Ant T	...	100	...	...	...	75	...	0.33	−0.10	47	+9	0	↓1	0	+	+	0	0	0
28	Ant T	...	99	90	99	75	99	...	0.27	−0.07	61	+8	0	↑1	+	0	0	0	0	0
29	Inf T	...	90	60	99	...	80	...	0.42	−0.03	55	+7	0	↓2	0	0	0	+	0	+
30	Inf T	...	...	75	100	...	100	...	0.40	−0.08	63	+11	0	↓1	+	0	0	0	0	0
31	Inf T	...	95	...	100	...	100	...	0.40	−0.11	52	+16	0	↓1	0	0	0	+	0	+
32	Inf T	...	90	90	99	...	100	...	0.44	+0.02	52	+1	+	0	0	+	0	0	0	+
33	NT	...	75	60	95	...	50	...	0.45	−0.08	51	+24	0	↓2	0	0	0	+	+	0
34	NT	...	100	...	75	90	100	...	0.53	+0.01	35	+3	0	0	0	0	0	+	0	+
35	NT	...	25	50	100	...	100	...	0.47	+0.04	64	−4	+	0	0	+	0	0	0	+
36	NT	...	90	99	...	...	75	...	0.64	−0.05	21	+5	0	0	+	0	0	0	0	0
37	NT	...	90	...	90	50	...	...	0.56	+0.07	34	−3	0	0	0	0	0	0	0	0
38	Ant T	...	100	...	...	...	100	...	0.33	−0.12	64	+10	0	↑2	0	0	0	+	0	0
39	NT	...	...	50	100	...	90	...	0.37	−0.01	117	+1	0	0	0	0	0	0	0	0
40	NT	...	...	60	99	...	100	...	0.42	0	76	+12	0	↓1	0	0	+	0	0	+
41	Inf T	...	80	50	50	...	100	...	0.65	−0.17	43	+27	+	↓2	0	0	0	+	0	+
42	NT	...	75	...	99	...	75	...	0.38	0	70	+13	0	↓2	0	0	0	0	0	0

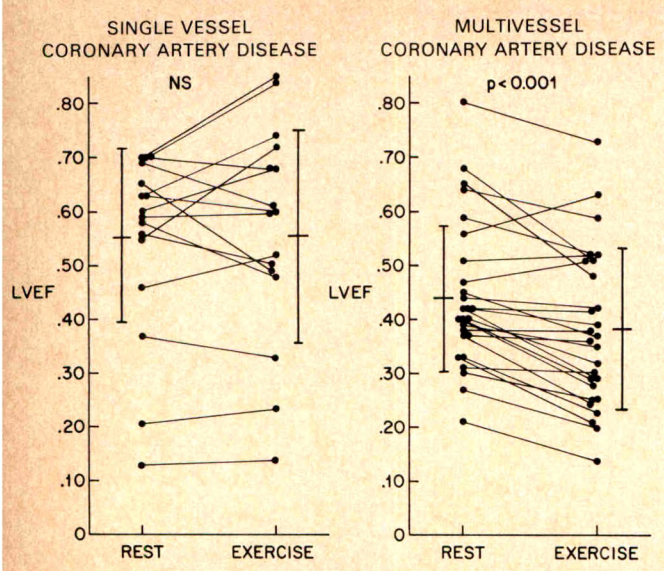

FIGURE 2. Response of the left ventricular ejection fraction (LVEF) to exercise in patients with single or multivessel coronary artery disease after acute myocardial infarction. In the group with single-vessel disease, LVEF changed from 0.55 ± 0.17 at rest to 0.56 ± 0.20 at peak exercise (difference not significant [NS]). The group with multivessel disease showed a decrease in LVEF from 0.44 ± 0.14 at rest to 0.38 ± 0.15 at peak exercise ($p < 0.001$).

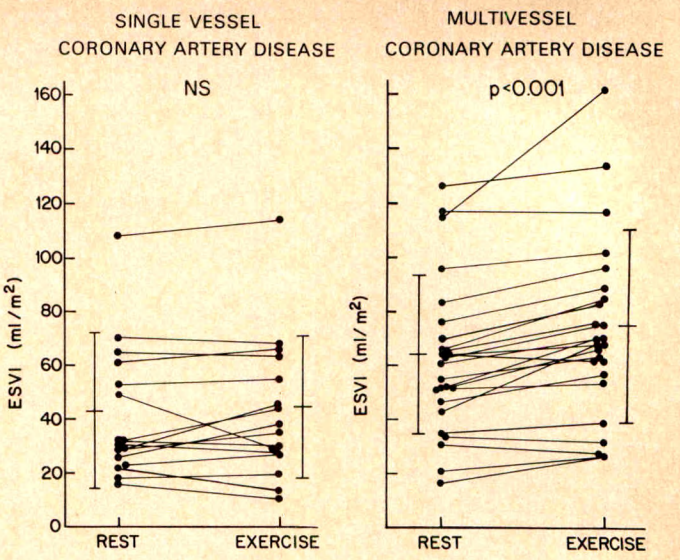

FIGURE 3. Response of the left ventricular end-systolic volume index (ESVI) in patients with single (**left panel**) or multivessel (**right panel**) coronary artery disease. In the group with single-vessel disease, left ventricular ESVI changed from 42 ± 25 ml/m² at rest to 43 ± 26 at peak exercise (difference not significant [NS]). In those with multivessel disease, left ventricular ESVI increased from 63 ± 28 ml/m² at rest to 76 ± 37 at peak exercise ($p < 0.001$).

compared with the prognostic value of the LVEF response to exercise). An increase in LVESVI by >5% in response to exercise predicted the correct outcome in 11 patients (difference not significant compared with the prognostic value of the LVEF response). In the 26 patients with multivessel coronary artery disease, the subsequent course was correctly predicted in 25 by LVEF response to exercise, in 13 by resting LVEF ≤0.40 ($p < 0.001$ compared with LVEF response to exercise), in 20 by resting LVEF <0.55, and in 20 by an increase in LVESVI by >5% in response to exercise ($p = 0.10$ compared with LVEF response to exercise). Thus, both in patients with single and in those with multivessel coronary artery disease, the LVEF response to exercise may provide more prognostic information than mere knowledge of resting LVEF.

Segmental wall motion analysis: In response to exercise, patients with 2- or 3-vessel disease tended to have more wall motion abnormalities at sites adjacent to or remote from resting wall motion abnormalities than patients with single-vessel disease (Table I). However, there was considerable overlap between the 2 groups so that segmental wall motion abnormalities during exercise could not be used to differentiate patients with single and multivessel disease.

Discussion

Techniques aimed at assessing residual cardiac function after MI have helped define groups of patients at high or low risk after this event. However, some patients may have well-preserved myocardial function at rest and still have major complications. Such patients probably have regions of viable myocardium at risk of further ischemic damage. Exercise testing, with or without radionuclide techniques, and coronary angiography have both been proposed as means of identifying such patients.[14–22] We previously reported the prognostic value of a wide variety of patient-related variables after acute MI in an unselected group of patients using stepwise discriminant analysis.[14] Although the value of submaximal exercise testing with radionuclide ventriculography was demonstrated in this study, coronary angiographic information was not available for this unselected group of patients. Therefore, the relation between radionuclide determined variables and coronary angiographic findings after MI, and the relation of both these variables to the subsequent course, could not be assessed.

In our selected group of patients, those with multivessel disease had a poor prognosis after MI, as has been reported by other investigators.[23–26] These patients had an almost uniformly abnormal response to exercise. Those with single-vessel coronary artery disease generally had a better prognosis; however, some had subsequent major cardiac events. Although depressed resting left ventricular function, when present, was generally associated with a poor outcome, it was not a sensitive predictor of subsequent cardiac events. Conversely, functional alterations during exercise detected most of the patients with a complicated clinical course irrespective of whether they had single or multivessel disease. Therefore, functional alterations during exercise after MI may be a better prognostic indicator than mere knowledge of coronary anatomy or residual left ventricular function.

Possible reasons for exercise-induced abnormalities of left ventricular function: In patients with multivessel disease, an abnormal response to exercise

after MI can be explained by ischemic dysfunction of remote areas of myocardium that are supplied by diseased coronary arteries and are at risk of further damage.[37] The explanation for the abnormal response to exercise in certain patients with single-vessel disease is less readily apparent, but may be due to several factors: (1) the MI may not have involved all the territory supplied by the diseased artery—a "border zone" of myocardium supplied by collateral vessels remains, which may become ischemic during increased myocardial oxygen demand, such as occurs during exercise; (2) the infarcted myocardium may cause a zone of akinesia or dyskinesia around which wall tension is increased, producing increased myocardial oxygen demand and diminished supply; (3) the extent of the disease process may be underestimated in the uninvolved arteries due to the diffuseness of the atherosclerotic process; and (4) coronary artery spasm may develop in uninvolved arteries during exercise.

Aneurysm formation and increased wall tension in the border zone of the infarct is an unlikely explanation because only 3 of 9 patients with single-vessel disease and an abnormal exercise test had an akinetic or dyskinetic area. Underestimation of the atherosclerotic process in uninvolved arteries is a possibility. Although coronary arterial spasm has been described during exercise,[38] it is probably uncommon. We believe that after MI, there may be a border zone of myocardium supplied mostly by collateral vessels, or residual flow, which is susceptible to further ischemia during periods of increased myocardial oxygen demand. However, this hypothesis awaits confirmation. Patients with single-vessel disease tended to have wall motion abnormalities during exercise confined to the site of MI, whereas patients with multivessel disease developed wall motion abnormalities at more distant sites.

Clinical implications and limitations of the study: The major limitation of this study is that it is a retrospective analysis of a select group of patients who underwent cardiac catheterization after MI, frequently because of a complicated clinical course. Therefore, it is not surprising to find a higher incidence of complications in our patients as a whole, and in particular in the subgroup with single-vessel disease, than has generally been reported in less selected groups of patients.[23–26] However, our data suggest that radionuclide ventriculography with submaximal exercise testing after MI provides valuable prognostic information not provided by mere delineation of coronary arterial anatomy or resting left ventricular function. A prospective study of a representative group of patients with single and multivessel coronary artery disease who undergo cardiac catheterization as well as rest and exercise radionuclide ventriculography will be necessary to confirm our findings.

Finally, our data suggest that every attempt should be made to protect those patients with exercise-induced deterioration in left ventricular function from further cardiac complications. Whether some or all of these patients with single- or multivessel coronary artery disease will benefit from revascularization or intensive medical therapy remains to be determined.

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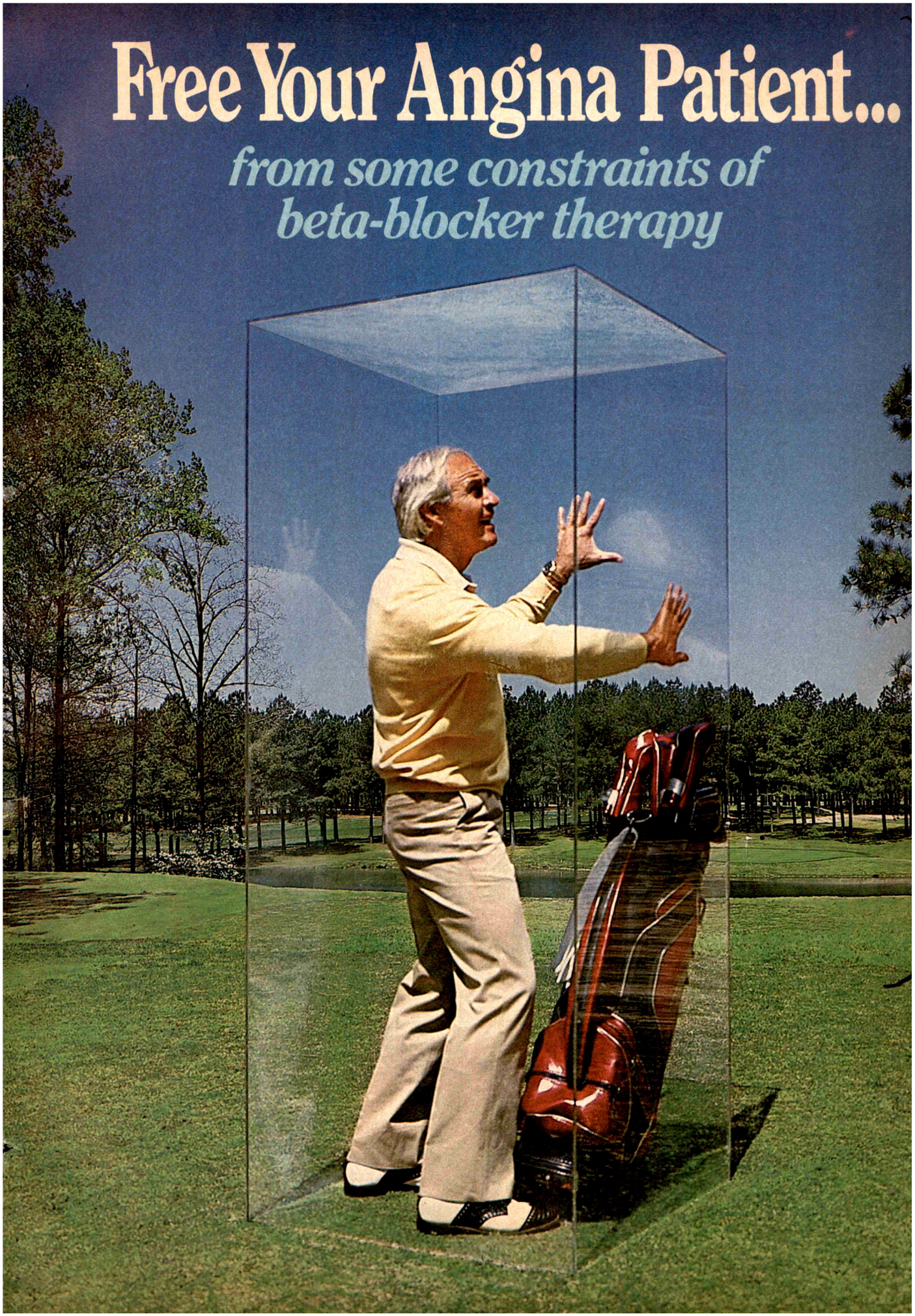
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Evaluation of a QRS Scoring System in Acute Myocardial Infarction: Relation to Infarct Size, Early Stage Left Ventricular Ejection Fraction, and Exercise Performance

YOSHIHIKO SEINO, MD, HOWARD M. STANILOFF, MD, WILLIAM E. SHELL, MD, DAVID MICKLE, RCPT, PREDIMAN K. SHAH, MD, and JOHN K. VYDEN, MB

Recent studies suggest that the QRS scoring system (QRSs) using observations of Q- and R-wave duration and R/Q and R/S amplitude ratios in the standard electrocardiogram (ECG) is useful in estimating left ventricular function after acute myocardial infarction (AMI).

The correlation of QRSs with infarct size determined by serum creatine kinase MB changes and early stage left ventricular ejection fraction (LVEF) determined by multiple gated equilibrium cardiac blood pool scintigraphy was studied in 32 patients with AMI using ECGs taken 3 and 7 days after onset. The relation of QRSs to exercise performance was also examined in 45 other patients who underwent heart rate limited low level exercise test (LLET) soon after AMI (12.3 ± 5.6 days, mean ± standard deviation).

The QRSs of 7 days after onset significantly correlated with both infarct size and LVEF; infarct size (CK·g·Eq) = 5.24 QRSs + 8.50 ($r = 0.72$, $p < 0.001$), LVEF (%) = −2.16 QRSs + 59.58 ($r = -0.71$, $p < 0.001$).

Patients with exercise tolerance of <6 minutes had significantly higher QRSs than patients wit exercise tolerance of 6 to 12 minutes or >12 mi utes (9.0 ± 3.3 versus 4.5 ± 2.4 and 3.6 ± 2.2, <0.001, respectively). All patients with QRSs < (24 of 45 patients) achieved exercise tolerance >5 minutes, whereas all patients who could n exercise for >5 minutes (10 of 45 patients) ha QRSs >5.

The relation between QRSs and the reasons fo termination of LLET showed that patients with fa tigue or dyspnea, or both, had significantly highe QRSs (8.7 ± 4.6) than those in target heart rate (5. ± 2.2, $p < 0.05$) and those in completed protoc (3.0 ± 1.7, $p < 0.01$), whereas patients with ches pain had intermediate QRSs (5.3 ± 2.7). The QRS was significantly higher in patients with S-T change during LLET (8.2 ± 4.5 versus 4.7 ± 2.8, <0.05).

These data suggest that QRSs will be clinicall useful not only as a variable correlating with infarc size and LVEF but also as an aid in early identif cation of exercise performance soon after AMI.

Primary loss of functioning myocardium is the most important cause of pump failure, and the amount of residual functioning myocardium is the major determinant of cardiac function in acute myocardial infarc tion (AMI).[1,2] Therefore, the evaluation of infarct siz and residual cardiac function has become essential i the treatment of patients with AMI.

To assess cardiac function, hemodynamic variable are monitored with a Swan-Ganz thermodilutio catheter or cardiac nuclear ventriculography is useful.[3] To assess residual cardiac function, the low level exe cise test is performed safely soon after AMI.[6–8]

Estimation of infarct size has been attempted b techniques such as analysis of changes in serum creatin kinase (CK),[9–11] nuclear ventriculography,[12–14] an

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analysis of electrocardiographic changes.[15–17] As the first 2 techniques have limitations in cost and availability, further investigations can be expected for possible establishment of the electrocardiographic method.

Recent studies by Palmeri et al[18] and Wagner et al[19] suggest the clinical usefulness of their QRS scoring system using standard 12-lead electrocardiograms to assess left ventricular function in patients with previous myocardial infarction.

The present study was performed to investigate the clinical values of their QRS scoring system (QRSs) in the early stage of AMI in terms of (1) how QRSs actually correlates with enzymatically estimated infarct size and early stage left ventricular ejection fraction (LVEF) determined by cardiac blood pool scintigraphy, and (2) relation to exercise test results soon after AMI.

Methods

Patients: This study consisted of 2 groups of patients, both having a first transmural AMI; the correlation studies investigated 42 patients (8 women, 34 men, aged 27 to 83 years, average 61.8) to determine the correlation between QRS score, enzymatically estimated infarct size, and early stage LVEF. The exercise performance study investigated 45 patients (11 women, 34 men, aged 30 to 86 years, average 60.9) to study the relation between QRS score and exercise performance soon after AMI.

TABLE I QRS Scoring System[18,19]

Lead	Q-Wave Duration (ms)		R-Wave Duration (ms)	Amplitude Ratios	Points	Maximum
I	≥30				1	
				R/Q ≤1	1	2
II	≥40				2	
	≥30				1	2
aV_L	≥30				1	
				R/Q ≤1	1	2
aV_F	≥50				3	
	≥40		•		2	
	≥30				1	
				R/Q ≤1	2	
				R/Q ≤2	1	5
V_1	Any				1	
			≥50		2	
			≥40		1	
			. . .	R/S ≥1	1	4
V_2	Any	or	≤20		1	
			≥60		2	
			≥50		1	
				R/S ≥1.5	1	4
V_3	Any	or	≤30		1	1
V_4	≥20				1	
				R/Q or R/S ≤0.5	2	
				R/Q or R/S ≤1.5	1	3
V_5	≥30				1	
				R/Q or R/S ≤1	2	
				R/Q or R/S ≤3	1	3
V_6	≥30				1	
				R/Q or R/S ≤1	2	
				R/O or R/S ≤3	1	3

The diagnosis of transmural AMI was based on the presence of all of the following criteria: (1) prolonged chest pain beyond 30 minutes, (2) development of a new Q wave with S-T elevation, and (3) characteristic elevation of serum CK including MB isoenzyme fraction, glutamic oxaloacetic transaminase, and lactic dehydrogenase. Patients with a history or electrocardiographic evidence of previous myocardial infarction or significant valvular disease were excluded from this study. Also, patients undergoing intraaortic balloon pumping, cardiac pacing, or intracoronary thrombolysis were excluded.

The anterior or inferior location of AMI was characterized according to established electrocardiographic criteria.[20] Of 42 patients in the correlation study, 27 had anterior and 15 had inferior MI, whereas in 45 patients in the exercise performance study, 18 had anterior and 27 had inferior MI.

QRS scoring system[18,19]: For this study, electrocardiograms taken 3 and 7 days after the onset of symptoms were used for QRS scoring in the correlation study. In the exercise performance study, resting control electrocardiograms taken at low level exercise testing were used for scoring.

Standard 12-lead electrocardiograms were scored according to the QRS scoring system based on the accumulation of a point score designed to estimate infarct size, as described by Palmeri et al[18] and Wagner et al.[19] The criteria for scoring are applied to each of 10 leads (I, II, aVL, aVF, and V_1 to V_6) and are derived from Q- and R-wave duration and R/Q and R/S amplitude ratios (Table I). All electrocardiograms were scored by 2 cardiologists independently without knowledge of the tracing's origin and of the results of other studies. If the 2 cardiologists scored differently, the third cardiologist determined the final score. If right or left bundle branch block, nonspecific intraventricular conduction delay (QRS ≥110 ms), or left anterior fascicular block (QRS axis ≤ −60°) was present on the electrocardiogram, the patient was excluded from QRS scoring.[18,19]

Measurement of infarct size by CK-MB: Serum CK-MB levels were determined by column chromatography as previously described by Shell et al.[21,22] Infarct size was computed by analysis of serum CK-MB changes using the formula of Sobel,[9] Shell[10] and their associates.

Measurements of early stage LVEF[5,23]: Multiple gated equillibrium cardiac blood pool scintigraphy in the 45° left anterior oblique and anterior views was performed within 48 hours of the onset of symptoms, after injection of 20 to 25 mCi of in vitro labeled technetium-99m autologous red blood cells, using a mobile gamma camera (Ohio Nuclear 420) equipped with a low-energy all-purpose collimater and a mobile computer (Medical Data System). No patients were receiving digitalis, propanolol, vasodilators, or sympathomimetic agents at the time of the scintigraphic study. LVEF was determined semiautomatically from the background-corrected left ventricular activity-time course. LVEF = (end-diastolic counts − end-systolic counts)/end-diastolic counts.

Low level exercise test soon after AMI: The low level exercise test was performed before hospital discharge. Average time from AMI to exercise test was 12.3 ± 5.6 days (mean ± standard deviation). This study excluded patients with coronary bypass surgery or evidence of left heart failure (lung rales or gallop sounds). Each patient had a 12-lead electrocardiogram at rest as a control before starting the treadmill test. A CM_5 lead was placed and monitored continuously throughout the exercise test and for at least 5 minutes thereafter or until the electrocardiogram returned to baseline. Recorded electrocardiogram strips, heart rate, and blood pressure were taken each minute. Patients were exercised on a treadmill according to a modified Bruce protocol.[24,25] Cri-

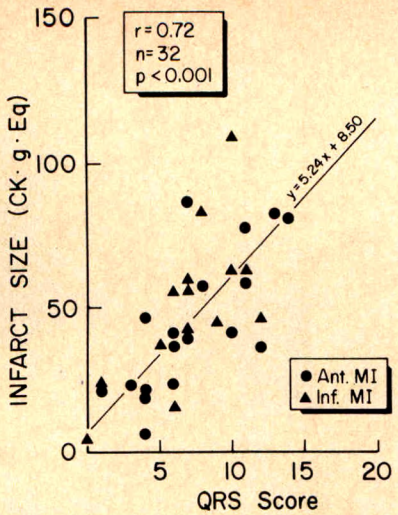

FIGURE 1. Correlation between QRS score and enzymatically estimated infarct size. Ant. MI = anterior myocardial infarction; Inf. MI = inferior myocardial infarction.

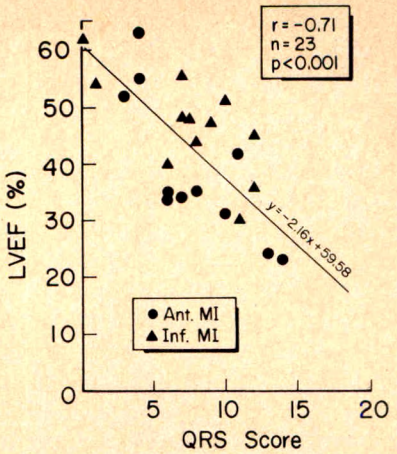

FIGURE 2. Correlation between QRS score and early stage left ventricular ejection fraction (LVEF). Abbreviations as in Figure 1.

teria for termination of the test were the development of chest pain, excessive fatigue or dyspnea, heart rate >120 beats/min (heart rate >100 beats/min in patients taking beta-blocking drugs), warning arrhythmias (premature ventricular contractions >6/min, R on T phenomenon), or METs >7 (equal to completion of the protocol).

Statistical analysis: All data are expressed as mean ± standard deviation. Pearson correlation coefficients between QRS score and enzymatically estimated infarct size and LVEF were obtained by simple linear regression analysis. The significance of difference in the QRS score between subgroups in exercise performance study was assessed using Kruskal-Wallis 1-way analysis of variance and Fisher's least significance difference. The QRS score in patients with and without exercise S-T changes was compared using the Mann-Whitney test.

Results

QRS score versus infarct size and early stage LVEF: Ten of 42 patients were excluded from QRS scoring because of right bundle branch block in 7, left bundle branch block in 1, and left anterior fascicular block in 2.

The QRS score 3 days after the onset of symptoms did not show any significant correlation with early stage LVEF nor enzymatically estimated infarct size. The QRS score 7 days after onset showed significant correlation with both early stage LVEF and infarct size.

The correlation between QRS score and enzymatically estimated infarct size is shown in Figure 1. Linear regression analysis demonstrated a significant correlation between QRS score and infarct size ($r = 0.72$, $n = 32$, $p < 0.001$). The equation for predicting infarct size from QRS score was: infarct size (CK·g·Eq) = 5.24 QRS score + 8.50.

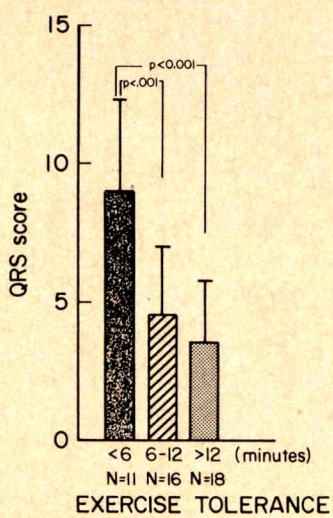

FIGURE 3. Relation between exercise tolerance and QRS score.

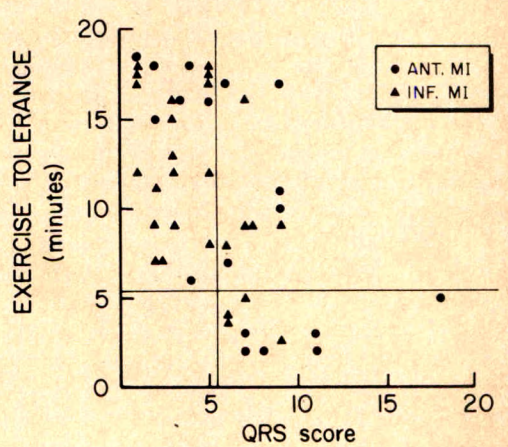

FIGURE 4. Relation between exercise tolerance and QRS score. Abbreviations as in Figure 1.

Similarly, the correlation between QRS score and early stage LVEF is shown in Figure 2. There was a significant inverse correlation between QRS score and LVEF ($r = -0.71$, $n = 23$, $p < 0.001$), with LVEF (%) = -2.16 QRS score + 59.58.

QRS score versus exercise performance: Of the 42 patients, 6 completed the protocol (achieved METs >7), 39 patients could not complete the protocol because of target heart rate (22 patients), chest pain (9 patients), excessive fatigue or dyspnea, or both (7 patients), and frequent premature ventricular contractions (1 patient). Six patients showed S-T depression >1.0 mm and 1 patient had S-T elevation >1 mm during low level exercise tests.

Figure 3 shows the relation between exercise tolerance and QRS score in these patients. Patients with exercise tolerance <6 minutes had a significantly higher QRS score compared with those with exercise tolerance 6 to 12 minutes or more (9.0 ± 3.3 versus 4.5 ± 2.4 and 3.6 ± 2.2, $p < 0.001$, respectively). Figure 4 also shows that all patients with a QRS score <6 achieved exercise tolerance >5 minutes, whereas all patients who could not exercise >5 minutes had a QRS score >5.

The relation between QRS score and reasons for termination of the test is shown in Figure 5. Patients with fatigue or dyspnea, or both, had a significantly higher QRS score compared with those in target heart rate and those in completed protocol (8.7 ± 4.6 versus 5.4 ± 2.2 and 3.0 ± 1.7, $p < 0.05$ and $p < 0.01$, respectively), whereas chest pain had an intermediate QRS score (5.3 ± 2.7).

Regarding the relation between QRS score and S-T segment changes during low level exercise testing, patients showing S-T changes during the exercise test had a significantly higher QRS score than did patients with no S-T changes (8.2 ± 4.5 versus 4.7 ± 2.8, $p < 0.05$).

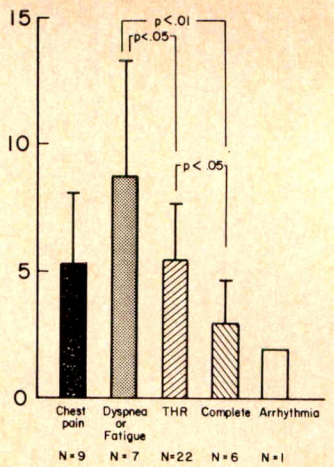

FIGURE 5. Relation of QRS score to reasons for termination of low level exercise test soon after acute myocardial infarction. THR = target heart rate.

Discussion

Electrocardiographic assessment of left ventricular function in AMI: Correlations between left ventricular function and changes in the QRS complex in electrocardiograms have been demonstrated. Awan et al[26] demonstrated a significant correlation between the number of pathologic Q waves in a 35-lead precordial mapping and LVEF in patients with anterior AMI. Askenazi et al[27] reported a significant correlation between the sum of R-wave amplitude in a standard electrocardiogram and LVEF in patients with chronic coronary artery disease. In the present study, a recently developed QRS scoring system using standard 12-lead electrocardiograms was studied; this system was established by Palmeri et al[18] and Wagner et al[19] based on computer simulation of sequence in the ventricular activation process.[28–30]

In their first clinical study, they manifested significant correlations between QRS score and LVEF using electrocardiography and radionuclide ventriculography taken 3 and 8 weeks after the onset of AMI. In their most recent study,[31] they correlated QRS score with pathologic infarct size in patients with anterior MI and demonstrated a significant correlation between QRS score and percent infarction of the left ventricle.

Our results magnify the clinical values of their QRS scoring system. QRS scoring using electrocardiograms taken 7 days after the onset of AMI has also significantly correlated with both early stage LVEF and enzymatically estimated infarct size. It seemed to be more reasonable and clinically available.

As for early stage LVEF in AMI, Shah et al[5] demonstrated its clinical value as a prognostic indicator, predicting hospital morbidity and mortality from pump failure. Although it was not the principal object in the present study, short-term follow-up (6 to 15 months) of 42 patients in the correlation study revealed that 10 patients died in this follow-up period; in 4 of these patients the QRS scores were 5, 7, 12, and 13, and intraventricular conduction delay was present in the other 6 patients. In these 10 patients, 6 had early stage LVEF <30%. Shah et al[5,23] reported that death because of pump failure occurred at a higher rate (>50%) in patients with early stage LVEF <30%. We confirmed a similar finding in the present study.

Regarding the prognostic implications of electrocardiograms after myocardial infarction, the Coronary Drug Project Research Group[32] reported that the presence of abnormal Q waves, S-T displacements, intraventricular conduction delay, or arrhythmias, or a combination of these, in resting electrocardiograms was importantly related to mortality over a 3-year follow-up period. Wasserman et al[33] also recently reported that patients with multiple Q-wave locations or with Minnesota Code major criteria of infarction based on Q-wave duration and Q/R amplitude ratios had significantly higher mortality rates during a 3-year follow-up period. Their reports agree with our follow-up observations. Further studies are required to determine the prognostic value of the QRS scoring system in AMI.

A number of studies have examined the correlation between enzymatically estimated infarct size and LVEF,[34,35] cardiac hemodynamics, or prognosis.[9,36–38] However, the present study is the first to document that the QRS scoring system by Palmeri, Wagner and their group[18,19] also correlated well with the enzymatically estimated infarct size in patients with AMI. The advantage of this QRS scoring system is that it is inexpensive, readily accomplished using standard electrocardiograms, and universally available for assessing infarct size and LVEF.

QRS scoring and exercise performance soon after AMI: Furthermore, the relation of QRS scoring to exercise performance was revealed. The QRS score would be useful for early identification of patients with higher exercise tolerance, because all patients with a QRS score <6 achieved exercise tolerance >5 minutes in this study. Moreover, the QRS scoring was significantly related to the symptoms during low level exercise testing soon after AMI. From these results, it is presumed that patients with a higher QRS score would have limited exercise tolerance because of symptoms of dyspnea or fatigue or reaching target heart rate in the early stage.

Dillahunt et al[39] reported that the ability to exercise ≥5 minutes on the treadmill at 1 mph, 0% grade, identified single-vessel disease in most patients. In our study, angiographic correlation was not investigated, although our results agreed with their findings, namely, patients with a QRS score <6 (equal to exercise tolerance >5 minutes) would have a smaller infarct and a greater LVEF. Paine et al[40] reported the significant correlation between exercise tolerance and LVEF and also between exercise tolerance and angiographic scar size (percent of abnormally contracting segment) estimated from left ventriculography in patients with previous myocardial infarction. Further, Weld et al[41] revealed that shorter exercise tolerance was strongly associated with cardiac death in the first year of follow-up. QRS scoring would be clinically important in early identification of exercise performance and also for prognostic implications combined with exercise test results.

The findings that the QRS score was higher in patients with than in those without exercise S-T changes suggested that S-T changes during low level exercise testing would develop in patients with a larger infarct and a lower LVEF period. Starling et al[42] reported that coronary events after the first AMI were more common in patients with exercise-induced S-T changes, anginal pain, or an inadequate blood pressure response. Therefore, it is suggested that patients with a higher QRS score, shorter exercise tolerance, and exercise-induced S-T changes would be consistent with these patients who are at risk for a future cardiac event.

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Multiform Accelerated Idioventricular Rhythm in Acute Myocardial Infarction: Electrocardiographic Characteristics And Response to Verapamil

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Thirteen patients with acute myocardial infarction with multiform accelerated idioventricular rhythm (AIVR) occurring during the first 12 hours of monitoring in the coronary care unit are described. This arrhythmia, similar to the more common uniform AIVR, was intermittent, did not cause hemodynamic compromise, and was not related to more serious ventricular arrhythmias. There was no correlation between the bundle branch block pattern of the multiform AIVR and the electrocardiographic location of the myocardial infarction, but there was a perfect correlation between the frontal plane electrical axis of the multiform AIVR and the electrocardiographic location of the myocardial infarction. The presence of fusion beats between the different forms of AIVR suggests multifocality rather than multiformity.

Intravenous verapamil (3 to 5 mg bolus) was administered to 6 patients with multiform AIVR in whom the arrhythmias were persistent enough to allow the evaluation of the effect of verapamil on the arrhythmia. Verapamil caused no change in the rate of AIVR in 1 patient, but in a second patient it decreased the rate by 20 beats/min. In 4 patients, verapamil abolished the arrhythmia: in 2 patients carotid sinus pressure (induced sinus slowing) allowed the emergence of the AIVR at a lower rate, and in the remaining 2 patients the arrhythmia was not observed.

In the last 4 years we have evaluated patients admitted to our coronary care unit with acute myocardial infarction (MI) in whom accelerated idioventricular rhythm (AIVR) developed. In 13 cases a multiform variety of AIVR was observed. In this report we present our experience with multiform AIVR and compare it with the reported experience with the more common uniform AIVR. In addition, we administered intravenous verapamil to 6 patients with multiform AIVR in whom the arrhythmia was long enough to evaluate the effect of the drug.

Methods

The diagnosis of acute MI was based on a typical clinical history and enzymatic curve together with typical electrocardiographic changes including the development of pathological Q-waves. The MI was considered anterior when the electrocardiographic changes included precordial leads V_1 to V_4 (anteroseptal MI) and/or leads V_2 to V_6 (anterolateral MI), while inferior MI included leads II and III and aVF.

AIVR was defined according to established criteria[1] which included (1) a ventricular rhythm with a rate of 50 to 125 beats/min; (2) initiation with an escape beat, fusion beat, or a late premature depolarization appearing during a slowing phase of the sinus rhythm; (3) a regular R-R interval; (4) termination with a return to sinus rhythm with or without fusion beats. Multiform AIVR was diagnosed when at least 2 different QRS morphologies of AIVR were detected. Four cases were previously partially reported.[2]

Once AIVR was detected, patients were connected to a 3-channel electrocardiogram. All cases of multiform AIVR were evaluated for up to 12 hours in order to study its natural evolution. Electrocardiographic leads aVR, aVL, and aVF were used to define the characteristic QRS morphology of each form of AIVR recorded and for purposes of follow-up study. Lead aVR determined the bundle branch block (BBB) morphology of the AVIR,[3] after corroboration with lead V_1; a right BBB morphology was characterized by a dominant R-wave and a left BBB was characterized by a dominant S-wave. Leads aVL and aVF were used for axis determination. Left-axis deviation was characterized by a positive complex in aVL and a negative complex in aVF, and right-axis deviation was characterized by a negative QRS complex in aVL and a posi-

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tive QRS complex in aVF. Multiform AIVR was therefore divided into 5 morphologic subgroups: (1) right BBB and left-axis deviation morphology; (2) right BBB and right-axis deviation morphology; (3) left BBB and left-axis deviation morphology; (4) left BBB right-axis deviation morphology; (5) undetermined BBB or axis deviation morphology.

Verapamil was administered as an intravenous bolus of 3 to 5 mg under electrocardiographic and blood pressure control. In case of disappearance of the arrhythmia after the administration of verapamil, carotid sinus pressure was applied to induce sinus slowing and facilitate the emergence of the ectopic rhythm.

Results

Clinical characteristics: There are 11 men and 2 women with ages ranging from 40 to 79 years (mean 60). The acute MI was electrocardiographically located to the anterior wall in 4 patients, to the inferior wall in 5 patients, and to both walls in 4 patients.

Characteristics of multiform AIVR: Multiform AIVR was of transient duration, did not cause hemodynamic compromise, and was not associated with serious ventricular arrhythmias; therefore, in no case was there a need for medical treatment.

Multiform AIVR with 2 different morphologies was detected in 7 cases, with 3 different morphologies in 5 cases, and with 4 different morphologies in 1 case (Fig. 1A and 2). In patients with anterior MI, the observed multiform AIVR morphologies were of right or left BBB pattern and always with right-axis deviation. In patients with inferior MI, the observed multiform AIVR morphologies were of right or left BBB pattern and always with left-axis deviation. In patients with combined anterior and inferior MI, the observed multiform AIVR morphologies were of right or left BBB and with right- and left-axis deviation or in 1 case with undetermined axis.

Multiform AIVR was first seen 3 hours after admission to the coronary care unit but was widely distributed during the subsequent 9 hours of evaluation. Different forms of AIVR were seen independently at different times but generally the 2 or 3 different forms of AIVR were seen to interchange between them with or without the occurrence of fusion beats (Fig. 1 and 2). These fusion beats occurred between the ectopic focus and sinus rhythm or between the 2 forms of AIVR (Fig. 1).

Response to verapamil: Six patients received intravenous verapamil. The first patient received various boluses (with 5-minute intervals between boluses) of only 3 mg of intravenous verapamil. The low amounts of verapamil were given to preclude hemodynamic compromise. In this patient, no change in the rate of the AIVR was seen. The remaining 5 patients received a 3 to 5 mg bolus of verapamil. In 1 patient, a decrease of the rate of the AIVR of 20 beats/min was observed (Fig. 1). In the remaining 4 patients, the AIVR disappeared. After the administration of verapamil and the disappearance of AIVR, carotid sinus massage was applied to these 4 patients (induced sinus slowing or arrest) in order to avoid any possible overdrive suppression of the AIVR. In 2 patients, despite adequate slowing, AIVR

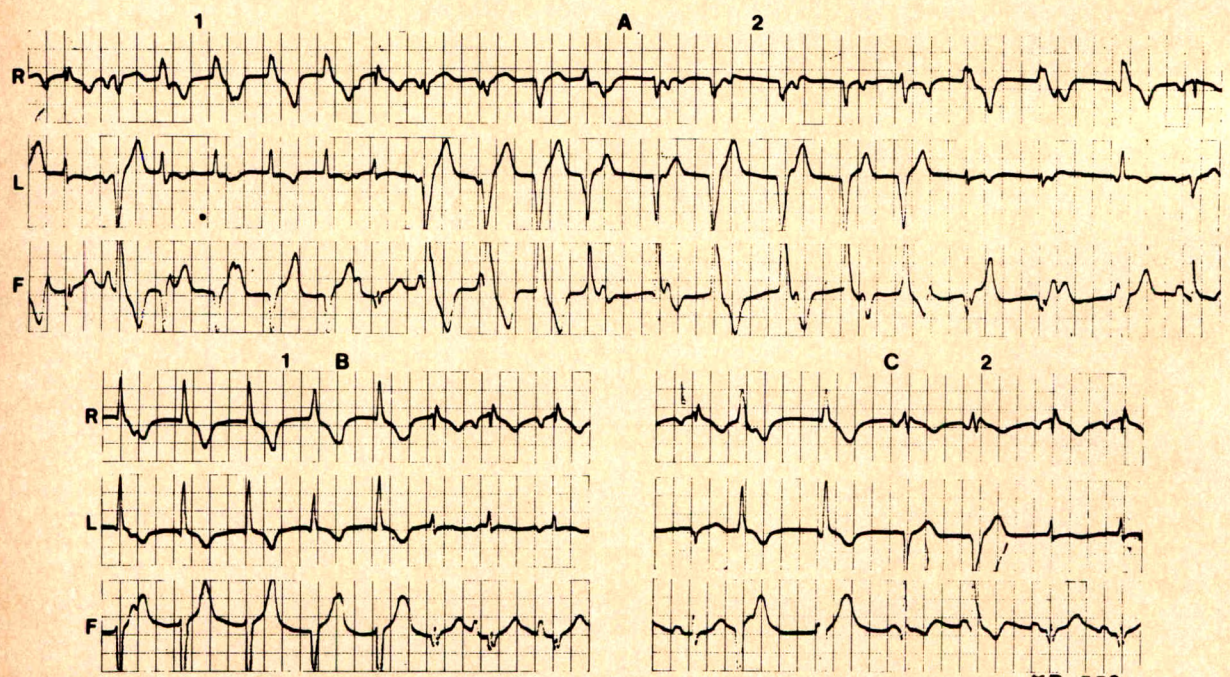

FIGURE 1. Example of multiform accelerated idioventricular rhythm (AIVR) of 2 different QRS morphologies and the effect of verapamil. All tracings were recorded with a 3-channel electrocardiogram with leads aVR, aVL, and aVF. **A**, 2 forms (1 and 2) of AIVR are observed. Form 1 has a right BBB morphology, left-axis deviation, and a rate of 100 beats/min. Form 2 has a left BBB morphology, right-axis deviation, and a rate of 95 beats/min. AIVR of form 1 changed to form 2 with the occurrence of a fusion beat between a sinus beat and AIVR form 1 (7th QRS of the strip). Subsequently, AIVR of form 2 reverted to form 1 with fusion beats between both forms (17th and 18th QRS of the strip). After the administration of verapamil (**lower panels**), AIVR of form 1 (**B**) is observed at a rate of 80 beats/min and AIVR of form 2 (**C**), which are fusion beats, are observed at a rate of 75 beats/min.

was not observed (Fig. 3). In the other 2 patients a similar form of AIVR, but at a slower rate, was observed once enough slowing of the sinus rhythm was obtained with carotid massage (Fig. 4).

Discussion

Uniform AIVR is an arrhythmia of ectopic ventricular origin occurring most commonly during the first 24 hours of an acute MI; its course is generally benign and there is no need for treatment.[4] We[5] reported on 2 patients with MI who had 2 different morphologies of AIVR. In both cases, the arrhythmia occurred during the first hour after admission to the hospital, and it had a transient nature and a benign course, similar to the course described for uniform AIVR. Since our initial observation, we have detected 13 additional patients with multiform AIVR. The reason for this is mainly the use of a 3-channel electrocardiogram with frequent recordings during the first 12 hours of the admission to the coronary care unit. The evolution observed for multiform AIVR was similar to the described evolution of uniform AIVR. The arrhythmia appeared during the first 24 hours of the MI, it had a transient duration, it did not cause hemodynamic compromise, and it did not degenerate or induce more serious ventricular arrhythmias. Therefore, as in uniform AIVR there seems to be no need for treatment.

The different morphologies of AIVR were scattered during the 12 hours of recording. Usually there was a predominant form of AIVR at 1 determined time of the recording. Once 1 form of AIVR would emerge and disappear, a lapse of several hours could be observed until the emergence of a second or third form of AIVR. When 2 forms of AIVR would compete for dominance of the heart rhythm, they usually interchanged with fusion beats between them. The fact that different forms of AIVR would appear several hours after the appearance of uniform AIVR indicates that multiform AIVR could indeed be a more common arrhythmia; many cases of uniform AIVR, if followed carefully and with 3-channel electrocardiographic recording, will show a multiform morphology. Additionally, it was of interest to observe fusion beats between different forms of AIVR. It has been demonstrated that different QRS morphologies could be the expression of different patterns of activation of a single ectopic foci.[6–9] Therefore, the term *multiform* is preferred to *multifocal.* Nevertheless, the presence of different degrees of fusion beats between these different AIVR forms suggest multifocality rather than multiformity. It is conceivable that different areas of abnormal automatism (expressed as AIVR) emerge simultaneously or at different times in the infarcted myocardium developing a multiform variety of AIVR.

Multiform AIVR morphology and acute MI location: The QRS configuration of ventricular ectopic beats has been used to try to determine its site of origin. In the absence of organic heart disease, the BBB pattern of premature ventricular complexes usually indicates the ventricle of origin.[10] In addition, the work of Mautner and Girotti,[11] Rosenbaum,[12] and Waxman and Josephson[13] suggests that the electrical axis of the ventricular premature beats are related to its site of origin. In ischemic heart disease, it has been demonstrated that the QRS configuration cannot be utilized to determine the site of origin of ventricular tachycardia.[8] Despite the above observation, in a previous study, we observed a 90% correlation between the origin of

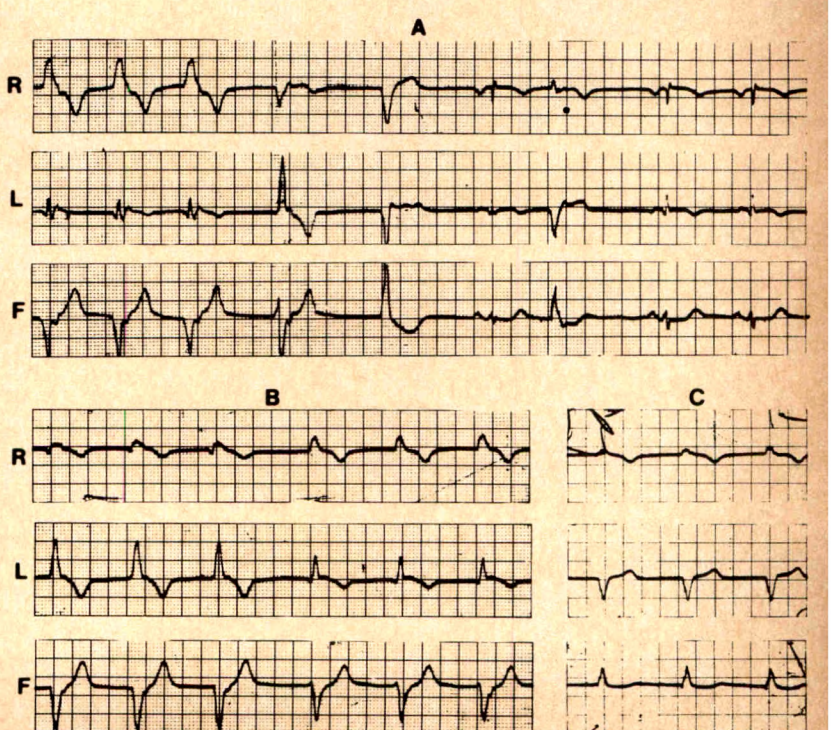

FIGURE 2. Example of AIVR with 4 different forms. **A**, the first 3 beats represent an AIVR with right BBB morphology and "undetermined axis." **B**, 2 additional forms of AIVR. Both forms have right BBB morphology and left-axis deviation, but they differ in the first QRS vector. **C**, the fourth form of AIVR with right BBB morphology and right-axis deviation.

premature ventricular contraction appearing during acute MI and the location of the infarction as determined by the electrocardiogram.[14] In the present study, the type of BBB of the multiform AIVR did not correlate with the electrocardiographic location of the acute MI, since virtually in all patients both right and left BBB morphologies were observed. In contrast, we observed a good correlation between the electrocardiographic site of the infarction and the electrical axis of the AIVR. In patients with acute inferior MI, the AIVR (irrespective of the BBB pattern) always had a left-axis deviation pattern suggesting an inferior origin of the ectopic rhythm; however, in patients with anterior MI, a right-axis deviation was observed, suggesting an anterior site of origin. In patients with combined MI, both right- and left-axis deviation were observed. The findings in our previous study of a relationship between premature ventricular contractions morphology and the electrocardiographic location of the acute MI and the finding in the present study of the relationship of AIVR morphology (axis deviation) and the electrocardiographic location of the acute MI suggests an origin for the ectopic ventricular rhythm in the area of acute MI.

Electrophysiologic features of AIVR and the effect of verapamil: AIVR occurs in the late arrhythmic phase (phase II) of acute MI.[4] The mechanism of AIVR is not clearly understood but it is postulated that abnormal automaticity in the subendocardial Purkinje fibers under the infarct is the responsible mechanism for this arrhythmia.[4] In addition, abnormal automaticity in acute MI has been related to the slow inward current[3,15] and therefore it could be expected to be suppressed by verapamil, a drug that mainly inhibits the slow inward current.

In this study, verapamil was administered to 6 patients with AIVR. In 1 patient no effect on the arrhythmia was observed. This patient received low boluses (3 mg) of verapamil because of fear of hemodynamic compromise. It is possible that with higher doses of verapamil, an effect on AIVR would have been apparent. In 5 patients, an effect of verapamil on AIVR was observed. In 1 patient a decrease in the rate of the AIVR was observed, and in the remaining 4 patients the arrhythmia disappeared. Carotid sinus massage was applied in all these responders; in 2 patients the same ectopic rhythm at a lower rate could be demonstrated and in the remaining 2 patients no ectopic rhythm was observed. The effect of verapamil on this arrhythmia is further evidence of the role of the slow inward current in the genesis of venticular arrhythmias during acute MI.

Clinical implication: AIVR is generally considered a benign arrhythmia, even though studies contradicting these results have been reported. Multiform AIVR is a variety of AIVR with identical pathophysiologic features and clinical course. We believe that the incidence of multiform AIVR is higher than expected and is related to type, length, and degree of monitoring. Since multiformity has been considered an indicator of the

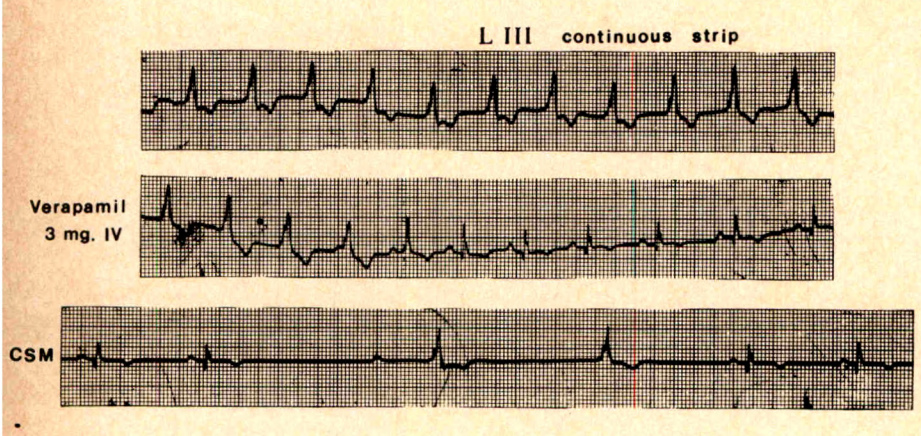

FIGURE 3. Administration of verapamil to a sustained bout of AIVR results in termination of the arrhythmia apparently due to sinus rhythm overdrive suppression, but carotid sinus massage (CSM) fails to uncover the presence of AIVR and shows 2 ventricular escape beats of morphology similar to the AIVR. IV = intravenous; LIII = lead III.

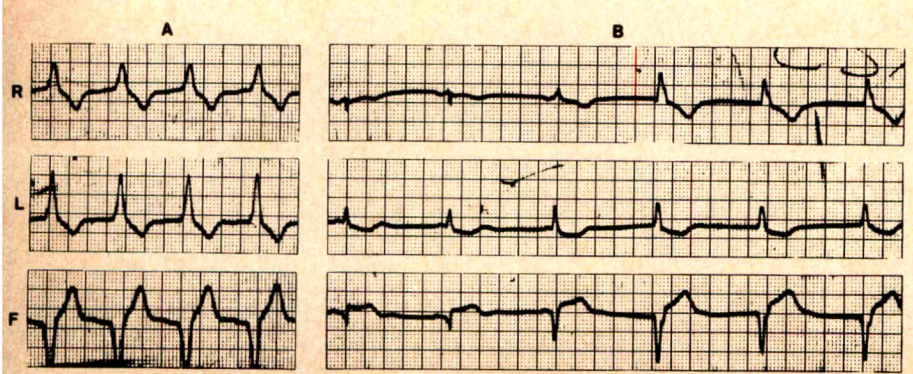

FIGURE 4. Effect of verapamil on AIVR. **A**, an episode of AIVR with a rate of 80 beats/min. Administration of verapamil resulted in disappearance of AIVR. Carotid sinus pressure (**B**) caused sinus slowing, allowing the emergence of a similar form of AIVR at a rate of 55 beats/min. F = lead aVF; L = lead aVL; R = lead aVR.

degree of severity and danger of premature ventricular contractions occurring during acute MI, it is worth emphasizing the benign nature of this multiform rhythm. Finally, the effects of verapamil on this rhythm offer new evidence of the role of the slow inward current in the genesis of arrhythmia occurring during acute MI.

Addendum

We administered verapamil to 2 patients (4 and 5 mg, respectively) with frequent and short bouts of uniform AIVR. In these cases, carotid sinus pressure reproducibly facilitated the emergence (due to sinus slowing) of the AIVR. After the administration of verapamil, application of carotid sinus massage caused a higher degree of sinus slowing but without the reemergence of AIVR.

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Subcostal 2-Dimensional Echocardiographic Imaging of Peripheral Left Coronary Artery Aneurysms in Kawasaki Disease

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Our previous study provided a new 2-dimensional echocardiographic technique to detect peripheral right coronary artery aneurysms in Kawasaki disease, with use of the subcostal approach. An additional study was performed to detect peripheral left coronary artery aneurysms. Because the left anterior descending artery runs along the anterior interventricular sulcus and the left circumflex artery along the mitral valve ring, these regions were searched for coronary aneurysms by use of the subcostal imaging approach. Among 143 patients with Kawasaki disease, 44 left coronary aneurysms were visualized in 22 patients. Three aneurysms at the origin of the obtuse marginal artery and 1 in the further peripheral site of the left circumflex artery were observed in 3 patients. Two aneurysms at the origin of the second diagonal branch of the peripheral left anterior descending artery were detected. These echocardiographic studies were done prospectively, and their features coincided well in size, shape, and anatomic location with confirmatory angiographic appearances.

Recognition of coronary aneurysms by noninvasive methods is useful in following up patients with Kawasaki disease because coronary aneurysm is an ominous complication that carries a risk of sudden death.[1–9] Two-dimensional (2-D) echocardiography can be used to visualize coronary aneurysms using the parasternal horizontal approach at the level of the aorta.[10–13] However, this approach visualizes only limited areas of the proximal segments of the coronary arteries. In our previous study, we described a technique for detecting peripheral coronary aneurysms of the right coronary artery.[14] In the present study, we describe a technique for detecting peripheral coronary aneurysms of the left coronary artery from the ostium to terminal sites in both the left anterior descending (LAD) and left circumflex (LC) arteries, using the subcostal approach.

Methods

Two-dimensional echocardiograms were recorded in 143 patients with Kawasaki disease (86 male and 57 female), aged 2 months to 8 years, whose conditions were assessed on the basis of guidelines prepared by the Japanese Research Committee in 1978. Coronary angiography was performed in 34 patients with Kawasaki disease: 31 patients were suspected of having coronary aneurysms on 2-D echocardiography. The other 3 patients had no positive findings on 2-D echocardiography but were severely affected on the basis of clinical features and laboratory data.

We performed this study using a real-time mechanical sector instrument (Aloka SSD 1000 with ASU 25 hand scanner and USM 6B amplifier). The scanner probe, which contained a 3 MHz transducer focused at 7.5 cm, was mechanically driven through a variable angle (30° to 80°) at a rate of 30 frames/s, yielding a line density of approximately 110 lines/frame. Two-dimensional echocardiographic images were observed in real time during the examinations. The images, which were displayed as phase-selected single frames, were photographed directly from the oscilloscope screen with a Polaroid® camera, and real-time images were recorded with a 16 mm cinecamera and analyzed subsequently in real-time, slow motion, and single format.

Anatomically, the left main coronary artery originates from the left coronary sinus and passes between the pulmonary trunk in the front and left atrial appendage behind. A short distance from its origin, usually a few millimeters in infants and children, it divides into LAD and LC arteries. The LAD artery passes downward over the anterior surface of the heart along the full length of the anterior interventricular sulcus and onto the inferior surface. The LC artery departs at an acute angle from the left main coronary artery to run posteriorly along the atrioventricular groove, toward the crux cordis.

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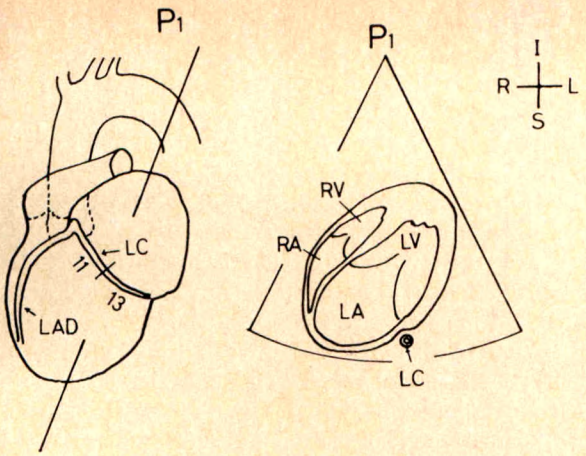


FIGURE 1. Schematic drawings of the subcostal view for imaging coronary aneurysms in segments 11 and 13 of the left circumflex artery. **Left,** the position of sector P1, showing a view of the 4 chambers. The left circumflex aneurysms can be detected at the left side of the mitral valve. I = inferior; L = left; LA = left atrium; LAD = left anterior descending artery; LC = left circumflex artery; LV = left ventricle; R = right; RA = right atrium; RV = right ventricle; S = superior; 11 and 13 = segments 11 and 13.

Throughout this course, the LC artery encircles the mitral valve ring.[15–17]

The subcostal approach that we developed for imaging peripheral coronary aneurysms of the left coronary artery consists of 2 parts. The first is a subcostal frontal approach (Fig. 1). The scanner probe was initially oriented so that the sector beam was directed through the heart on a plane parallel to a line between the patient's shoulders, allowing simultaneous visualization of the 4 chambers (sector P1).[18,19] In the section, the LC artery runs along the left side of the mitral valve ring. The scan plane was angled more posteriorly for imaging the peripheral site of the LC artery, that is, segment 13 (segment classification according to American Hea Committee Report[20]).

The second part is a subcostal sagittal approach (Fig. 2 The section was first positioned roughly parallel to a plan cutting both the long axes of the sternum and spinal colum allowing simultaneous visualization of the right ventricula outflow tract, pulmonary valves, interventricular septun mitral valve, and left atrium (sector P2).[21] Next, the secto plane was angled to the left as plane P3 in Figure 2. In secto P2 and P3, the peripheral LC artery (segment 13) runs alon the inferoposterior side of the mitral valve ring. By scannin sectors P2 and P3, the inferoposterior area of the mitral valv ring was examined for coronary aneurysms. Then the secto plane was tilted more to the left, with the left atrium ju disappearing, so that the left ventricular cavity was image in the short axis (sector P4). In this sector, the LC artery ca be seen running along the supraposterior side of the left ven tricle around the mitral valve ring, and the LAD artery run along the superior side of the interventricular septum. Th sector plane was tilted more to the cardiac apex (sector P so that the LAD runs along the superior side of the interven tricular septum.

Technical considerations involved in recording coronar aneurysms must be done with this subcostal sagittal approach Particularly in sectors P2 and P3, the interventricular septu must be differentiated from the tricuspid valve. The tricuspi valve will be imaged slightly angled to the right and can b distinguished by its shape and motion. Also, it would be ver helpful to use a peripheral vein contrast echo that distin guishes the tricuspid valve and interventricular septum, be cause the tricuspid valve would be filled with contrast echoe The mitral valve, which is posterior to the interventricula septum, would be differentiated from the other structures the heart by confirming the interventricular septum.

Results

Among 143 patients with Kawasaki disease, le coronary aneurysms were visualized in 22 patients b 2-D echocardiography, including the proximal seg ments. Concerning the peripheral left coronary arter

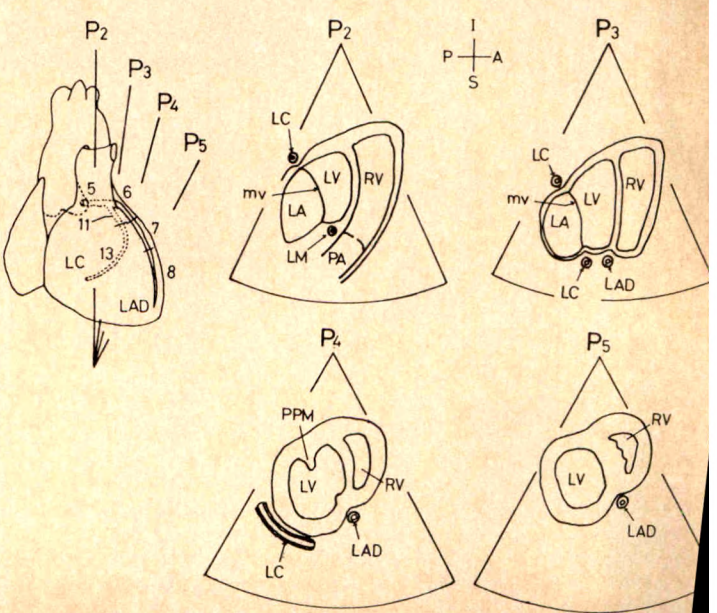


FIGURE 2. Schematic drawings of the subcostal views for imaging coronary aneurysms in segments 6, 7, and 8 of the left anterior descending artery and segments 11 and 13 of the left circumflex artery. The **top left panel** shows the position of sectors P2, P3, P4, and P5. Scanning from P2 to P4, coronary aneurysms of the left circumflex artery can be detected. Scanning from P3 to P5, coronary aneurysms of the left anterior descending artery can be detected. A = anterior; I = inferior; LA = left atrium; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main coronary artery; LV = left ventricle; mv = mitral valve; P = posterior; PPM = posterior papillary muscle; RV = right ventricle; S = superior; 5, 6, 7, 8, 11, and 13 = segments 5, 6, 7, 8, 11 and 13.

6 aneurysms (3 in the LC artery at the origin of the obtuse marginal artery, 1 in segment 13, and 2 in the LAD artery at the origin of the second diagonal branch) were detected with the subcostal approach. The echocardiographic findings of these 6 peripheral left coronary aneurysms almost coincided in size, shape, and anatomic position with angiographic features found later. However, coronary angiography, performed in all 34 patients suspected of having right or left coronary aneurysms, or both, by 2-D echocardiography and clinical findings, showed 2 aneurysms in segment 13 in 1 patient (Fig. 3). These 2 aneurysms were located at the origins of the posterolateral branch and the posterior descending branch and at first were regarded as 1 aneurysm in segment 13 by 2-D echocardography.

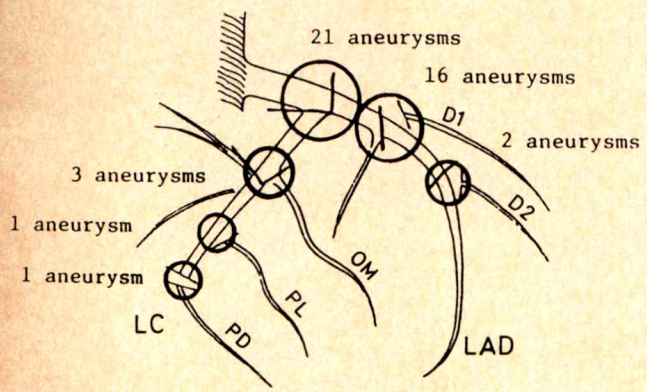
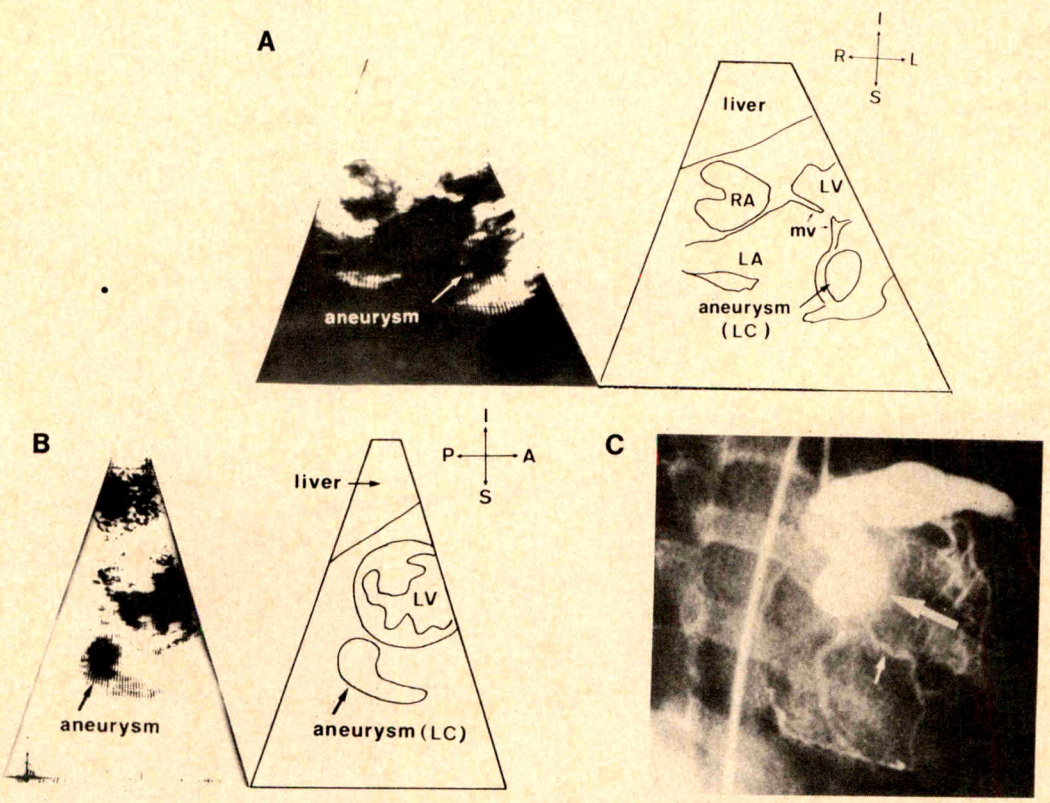


FIGURE 3. The number of left coronary aneurysms in each location by angiography. Forty-four left coronary aneurysms were shown in 22 patients with Kawasaki disease. D1 = first diagonal branch; D2 = second diagonal branch; LAD = left anterior descending artery; LC = left circumflex artery; OM = obtuse marginal artery; PD = posterior descending branch; PL = posterolateral branch.

Figure 4A, a 2-D echocardiogram in sector P1 from a patient with Kawasaki disease, shows an abnormal oval echo-free space, approximately 6 by 5 mm, at the left side of the mitral valve. This space was also imaged at the supraposterior side of the left ventricle around the mitral valve ring in sector P4 (Fig. 4B). The coronary aniogram (Fig. 4C) shows a coronary aneurysm at the origin of the obtuse marginal artery.

Figure 5A, a 2-D echocardiogram in sector P3 from a patient with Kawasaki disease, shows 3 abnormal echo-free spaces. One of these, approximately 4 by 4 mm, is seen at the inferior side of the mitral valve, adjacent to the liver. The coronary angiogram shows it to be a peripheral LC aneurysm in segment 13 (Fig. 5B). Another echo-free space, which the coronary angiogram (Fig. 5B) disclosed to be an aneurysm of the proximal LC artery, is visualized at the superior side of the mitral valve. The other echo-free space, which the coronary angiogram disclosed to be an aneurysm of the proximal



URE 4. Two-dimensional echocardiograms and coronary angiogram from a 1-year-old boy with Kawasaki disease. **A,** sector P1 showing an normal echo-free space (**arrow**) at the left side of the mitral valve. **B,** sector P4 showing the same coronary aneurysm as in **A. C,** angiogram wing 2 coronary aneurysms (30° right anterior oblique view). A coronary aneurysm (**large arrow**) at the origin of the obtuse marginal artery all **arrow**) corresponds to echo-free spaces in **A** and **B**. A = anterior; I = inferior; L = left; LA = left atrium; LC = left circumflex artery; LV = ventricle; mv = mitral valve; P = posterior; R = right; RA = right atrium; RV = right ventricle; S = superior.

LAD artery, is visualized at the superior side of the interventricular septum.

Figure 6A, a 2-D echocardiogram in sector P5 from a patient with Kawasaki disease, shows an oval echo-free space, approximately 3 by 2 mm, at the superior side of the interventricular septum. The coronary angiogram (Fig. 6B) shows a coronary aneurysm of the portion where the LAD artery branches off the second diagonal branch.

Discussion

Stenosis and obstruction of the coronary artery with Kawasaki disease, which carry a risk of sudden death, commonly occur in the front and rear of aneurysms. It is therefore important to recognize aneurysms in Kawasaki disease in order to determine the prognosis because stenotic and obstructive changes of the coronary artery cannot be easily visualized with 2-D echocardiography. It has been reported that the parasternal horizontal approach at the level of the aorta by 2-D echocardiography can visualize the proximal segment of the coronary artery.[10–13] However, this approach can image the coronary artery for only a few millimeters from the ostium. In a previous study, we described a new method of searching for peripheral right coronary aneurysms.[14] In the present study, we initiated a method of detecting peripheral left coronary aneurysm in both the LAD and LC arteries by using the subcostal approach. This method allowed the visualization of peripheral coronary aneurysms that could not be detected

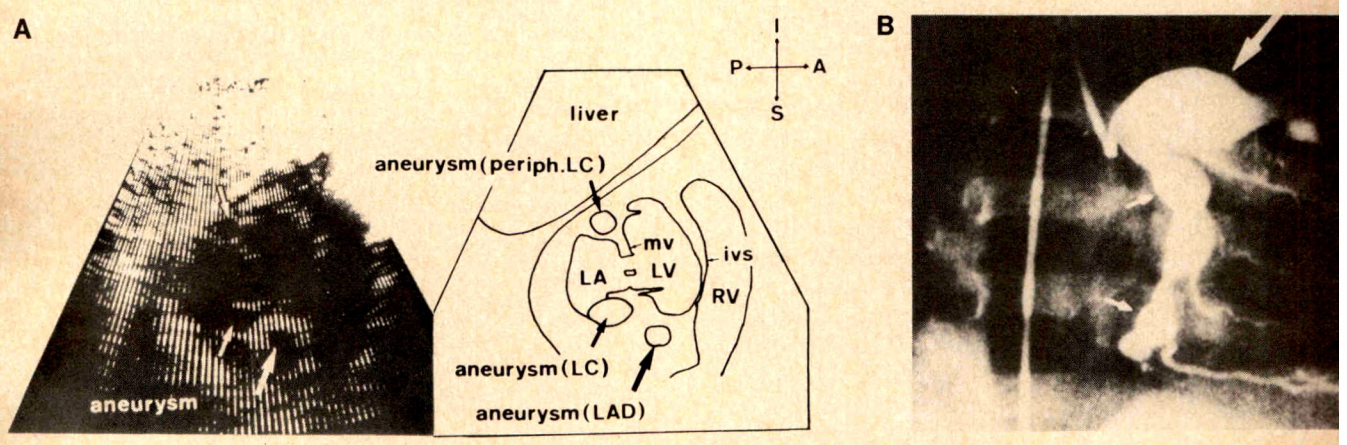
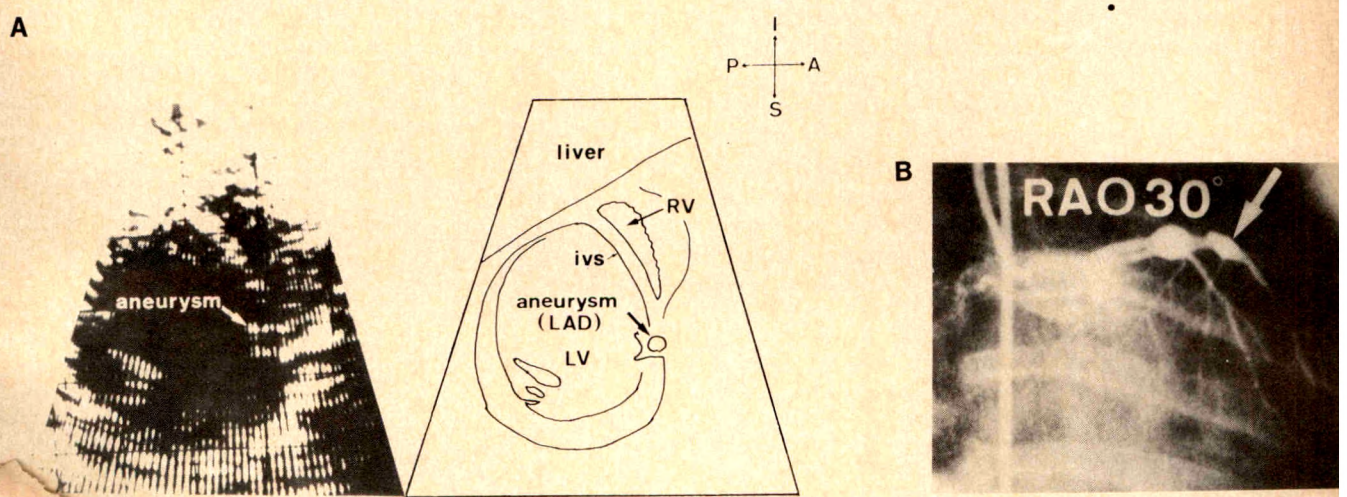


FIGURE 5. Two-dimensional echocardiogram and coronary angiogram from a 2-year-old boy with Kawasaki disease. **A,** sector P3 showing 3 abnorma echo-free spaces. One space is seen at the inferior side of the mitral valve (**upper small arrow**). Another is seen at the superior side of the mitra valve (**lower small arrow**). The other space is seen at the superior side of the interventricular septum (**large arrow**). **B,** angiogram showing severa aneurysms of the left coronary artery (30° right anterior oblique view). The **large arrow** corresponds to the **large arrow** in **A**. The **upper small arrow** corresponds to the **lower small arrow** in **A.** The **lower small arrow** corresponds to the **upper small arrow** in **A**. A = anterior; I = inferior; ivs = interventricular septum; LA = left atrium; LAD = left anterior descending artery; LC = left circumflex artery; LV = left ventricle; mv = mitral valve P = posterior; periph. LC = peripheral left circumflex artery; RV = right ventricle; S = superior.



Two-dimensional echocardiogram and coronary angiogram from an 8-month-old boy with Kawasaki disease. **A,** sector P5 showing a e space at the superior side of the interventricular septum. **B,** angiogram revealing 4 coronary aneurysms. A coronary aneurysm (**arrow** the left anterior descending artery branches off the second diagonal branch corresponds to an echo-free space in **A.** A = anterior entricular septum; LAD = left anterior descending artery; LV = left ventricle; P = posterior; RAO = right anterior oblique = superior.

with the parasternal horizontal approach. The images of the peripheral left coronary aneurysms, although not perfect, coincided well in size, shape, and anatomic position with the angiographic appearances later confirmed. With regard to the proximal segments, the parasternal horizontal approach is better than the subcostal approach because the former can detect coronary arteries on a long axis.

In this study, why the peripheral coronary aneurysms were not detected in the parasternal or apical approach without large aneurysms is an important question. The peripheral LAD aneurysms could be visualized using the parasternal short-axis view of the left ventricle at the level of the mitral valve papillary muscles. The parasternal short-axis view of the left ventricle at the level of the mitral valve ring and a parasternal or apical 4-chamber view should be useful for visualizing the peripheral portion of the LC artery. It is probable that we were not able to visualize peripheral coronary artery aneurysms in the parasternal views because we used a 3 MHz transducer focused at 7.5 cm. If we had used a transducer with a shorter focus, we might have been able to see these aneurysms from the precordial views.

Although the peripheral coronary artery, in normal infants and children, could not be visualized with the subcostal approach, we were able to image the dilatation of the peripheral LC artery (approximately 2 by 2 mm) because of Kawasaki disease in sectors P2 and P3. This technique may be limited in distinguishing small coronary aneurysms from the normal coronary artery because the peripheral segments of the left coronary artery are cut in slices. Therefore we had to obtain confirmation by angiography in all patients whose peripheral left coronary arterial echo-free spaces were visualized by subcostal approach. Because patients who underwent angiography were selected largely on the basis of their echocardiographic and clinical findings, we were unable to make any statements about false-negative results in the detection of peripheral coronary artery aneurysms. Further comparative studies with both echocardiography and coronary angiography may be required in many cases.

The parasternal horizontal approach is a good technique as it can image even the normal coronary artery on a long axis, but it can image only limited areas of proximal segments. Our previous study provided a technique for detecting peripheral right coronary aneurysms with use of the subcostal approach.[14] In the present study, we describe a new technique for detecting peripheral left coronary aneurysms in both LAD and LC arteries. By combining these 3 techniques, almost all coronary aneurysms, located in either the proximal or the distal artery, can be visualized with 2-D echocardiography.

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CME Test #1

Intracoronary Thrombus in Nontransmural Myocardial Infarction and in Unstable Angina Pectoris*

The University of Alabama School of Medicine designates this continuing medical education activity for 1 credit hou in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marke on instruction sheet on page 176.

1. Intracoronary thrombus clearly plays an important role in:
   a) acute transmural myocardial infarction
   b) nontransmural myocardial infarction
   c) unstable angina
   d) none of the above

2. Patients for this study were selected according to the presence of:
   a) an identifiable ischemia-related vessel
   b) bleeding diatheses
   c) hemorrhagic peptic ulcer disease
   d) recent cerebral vascular disease

3. Patients were selected who had:
   a) isolated coronary artery stenosis <60%
   b) isolated coronary artery stenosis >60%
   c) isolated coronary artery stenosis >70%
   d) had recent surgery

4. To determine percentages of stenosis, the narrowest stenotic diameter was compared with:
   a) the widest stenotic diameter
   b) the diameter of the nearest uninvolved distal segment
   c) the diameter of the nearest uninvolved proximal segment
   d) all the above

5. A positive anatomic response to nitroglycemia or streptokinase was defined as a conversion of:
   a) an occluded vessel to a simple obstruction
   b) an occluded vessel to a partial thrombotic block
   c) an occluded vessel to a patent vessel
   d) intraluminal filling defect

6. Thrombolysis was represented by and measurable with the defect index if there was at least a:
   a) ≥20% increase
   b) ≥40% reduction
   c) ≤20% reduction
   d) none of the above

7. Of 8 patients with nontransmural myocardial infarction, th number considered to have lysis of intracoronary thrombu was:
   a) 4 in response to nitroglycerin
   b) 5 in response to streptokinase
   c) 7 in response to nitroglycerin
   d) 7 in response to streptokinase

8. Of 9 patients with unstable angina, the number having positive anatomic response to:
   a) nitroglycerin, was 7
   b) streptokinase, was 7
   c) streptokinase, was 6
   d) streptokinase, was 4

9. In all instances, the changes were visible:
   a) to the patient
   b) under a microscope
   c) to the unaided eye
   d) none of the above

10. Measurements, providing quantitative documentation, es tablish that intracoronary thrombus does occur in som patients with:
    a) nontransmural myocardial infarction
    b) unstable angina
    c) both of the above diseases
    d) none of the above

11. Intermittent coronary spasms may be involved in nor transmural myocardial infarction and unstable angina be cause of:
    a) changes in patients with myocardial infarction
    b) absence of intracoronary thrombus
    c) changes in angina patients
    d) all the above

12. The specific clinical syndrome that results may be a functio of the:
    a) duration of obstruction
    b) size and extent of artery or branch involved
    c) available collateral circulation
    d) all the above

***This article appears on page 1 of this issue.**

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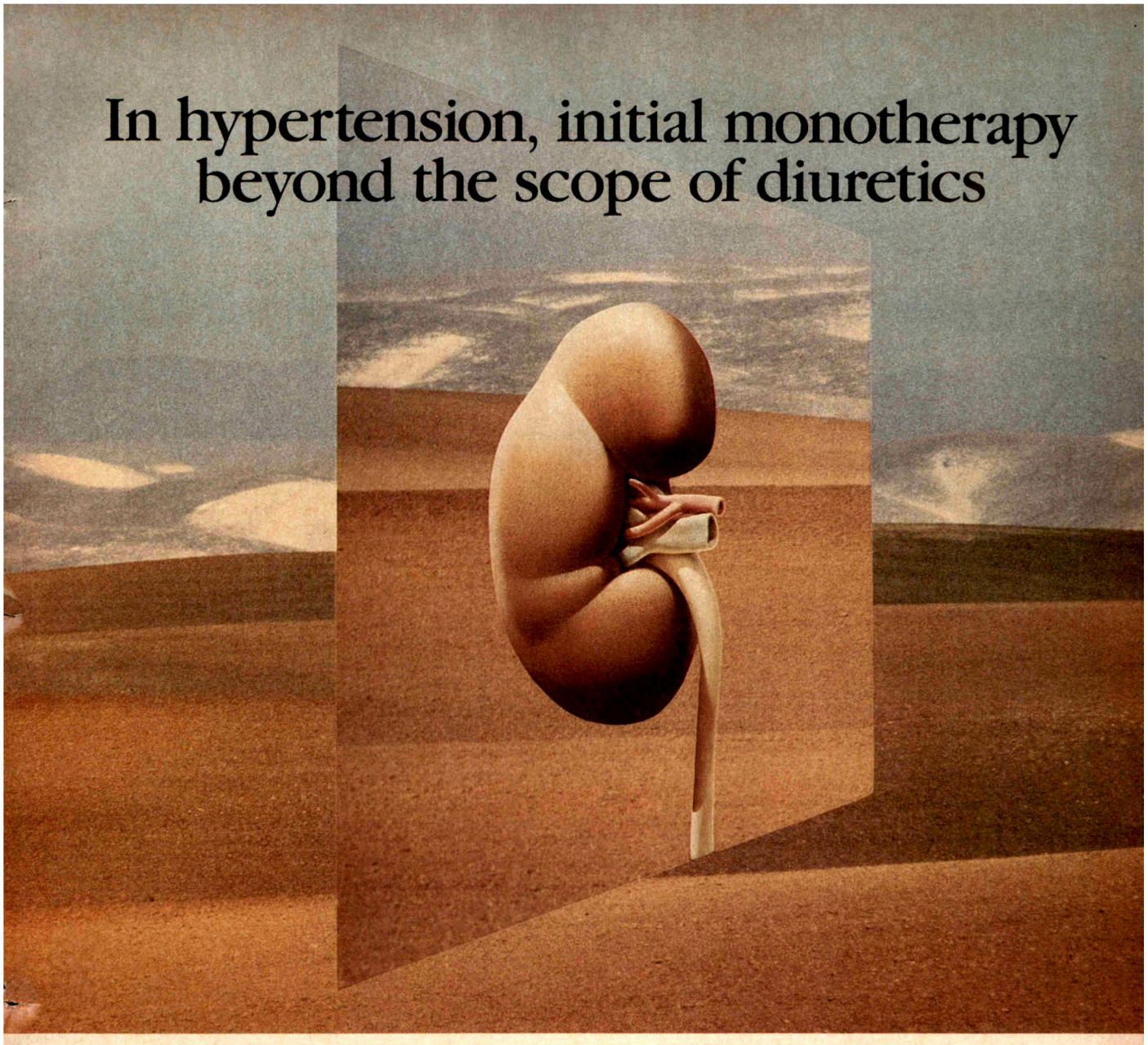

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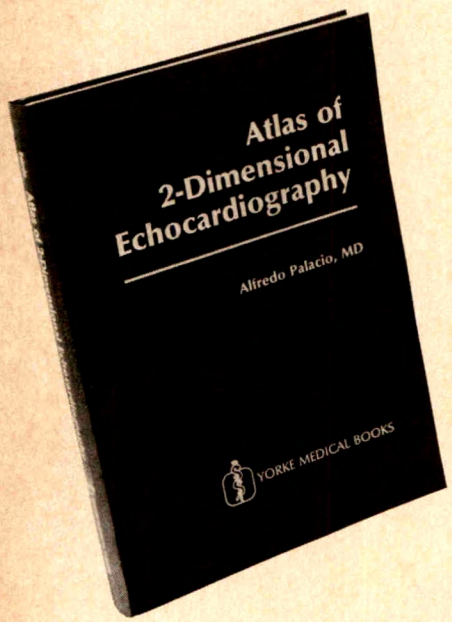

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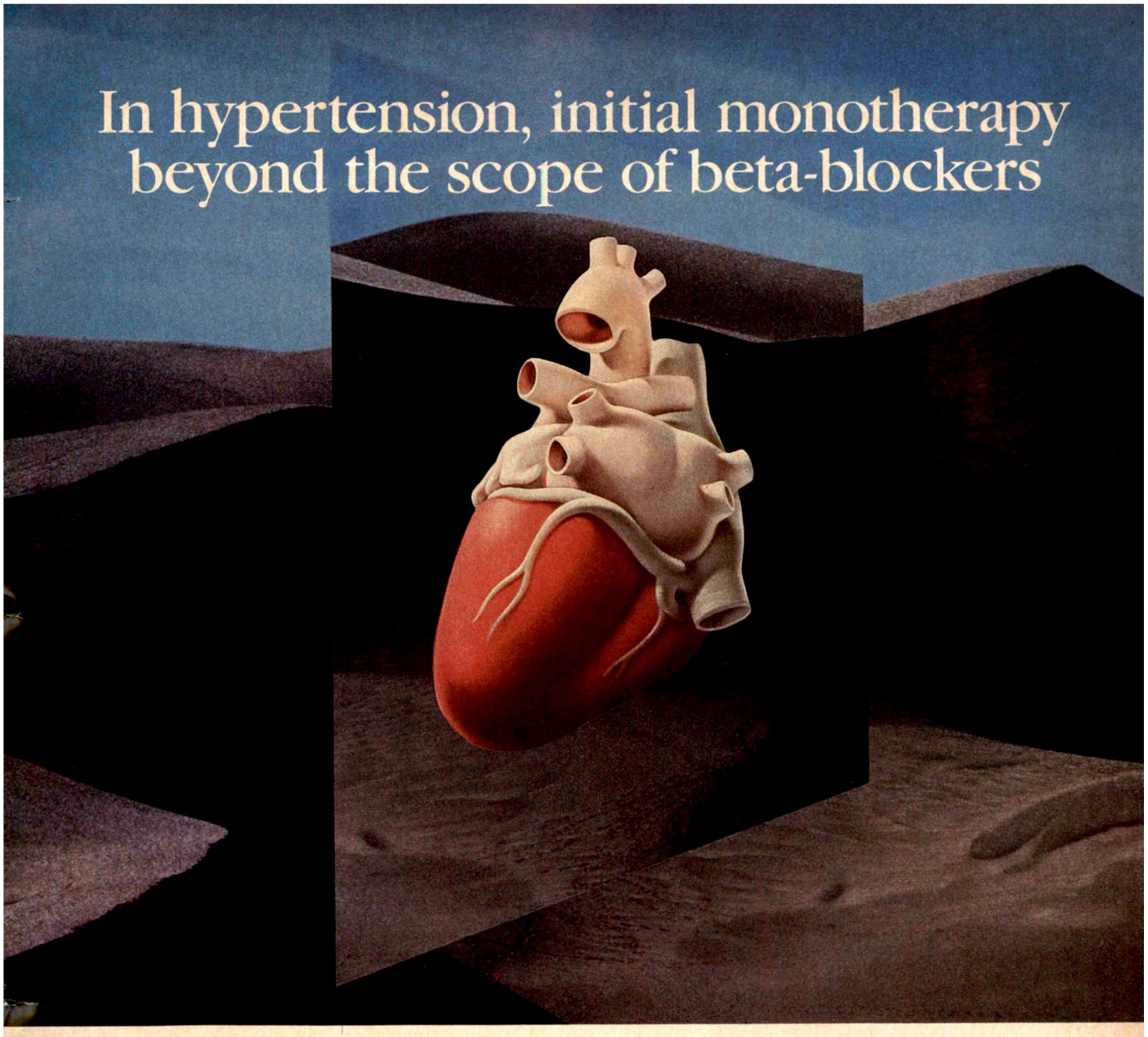

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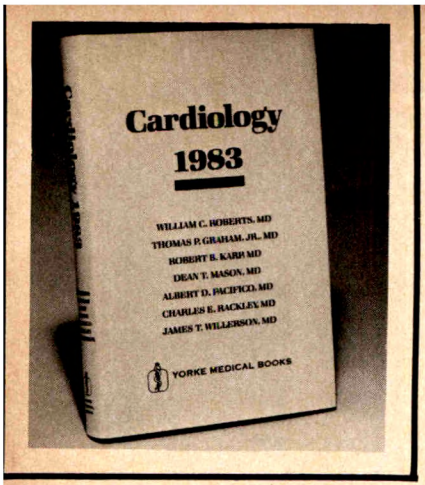

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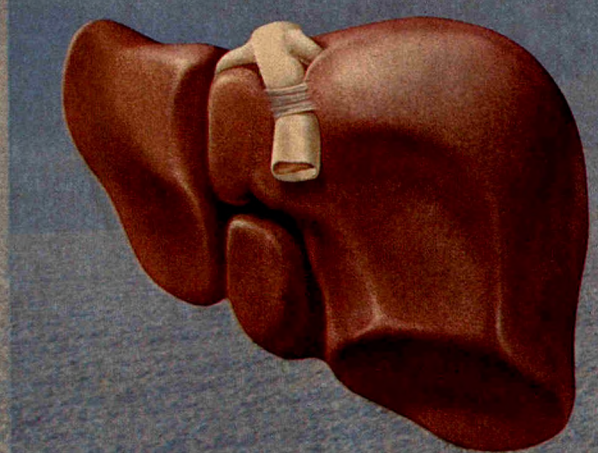

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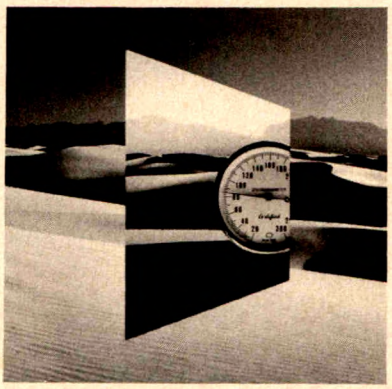

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Precautions:
1. Sedation: Causes sedation or drowsiness in a large fraction of patients. When used with centrally active depressants, e.g., phenothiazines, barbiturates and benzodiazepines, consider potential for additive sedative effects.

2. Patients with vascular insufficiency: Like other antihypertensives use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure.

3. Rebound: Sudden cessation of therapy with central alpha agonists like **Wytensin** may rarely result in "overshoot" hypertension and more commonly produces increase in serum catecholamines and subjective symptomatology.

INFORMATION FOR PATIENTS:
Advise patients on **Wytensin** to exercise caution when operating dangerous machinery or motor vehicles until it is determined they do not become drowsy or dizzy. Warn patients that tolerance for alcohol and other CNS depressants may be diminished. Advise patients not to discontinue therapy abruptly.

LAB TESTS:
In clinical trials, no clinically significant lab test abnormalities were identified during acute or chronic therapy. Tests included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term use there was small decrease in serum cholesterol and total triglycerides without change in high-density lipoprotein fraction. In rare instances occasional nonprogressive increase in liver enzymes was observed, but no clinical evidence of hepatic disease.

DRUG INTERACTIONS:
Wytensin® was not demonstrated to cause drug interactions when given with other drugs, e.g., digitalis, diuretics, analgesics, anxiolytics, and antiinflammatory or antiinfective agents, in clinical trials. However, potential for increased sedation when given concomitantly with CNS depressants should be noted.

DRUG/LAB TEST INTERACTIONS:
No lab test abnormalities were identified with **Wytensin** use.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
No evidence of carcinogenic potential emerged in rats during a two-year oral study with **Wytensin** at up to 9.5 mg/kg/day, i.e., about 10 times maximum recommended human dose. In the Salmonella microsome mutagenicity (Ames) test system, **Wytensin** at 200-500 mcg per plate or at 30-50 mcg/ml in suspension gave dose-related increases in number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae*, **Wytensin** produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats given high oral doses (9.6 mg/kg), suggesting impairment of fertility. Fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by decreased pregnancy rate of mates, even though females received drug only during last third of pregnancy.

PREGNANCY:
Pregnancy Category C:
WYTENSIN® MAY HAVE ADVERSE EFFECTS ON FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice indicated possible increase in skeletal abnormalities when **Wytensin** is given orally at doses 3 to 6 times maximum recommended human dose of 1.0 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral **Wytensin** given to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies in rats have shown slightly decreased live-birth-indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. **Wytensin®** should be used during pregnancy only if potential benefit justifies potential risk to fetus.

NURSING MOTHERS:
Because no information is available on **Wytensin** excretion in human milk, it should not be given to nursing mothers.

PEDIATRIC USE:
Safety and effectiveness in children less than 12 years of age have not been demonstrated; use in this age group cannot be recommended.

Adverse Reactions:
Incidence of adverse effects was ascertained from controlled clinical studies in U.S. and is based on data from 859 patients on **Wytensin** for up to 3 years. There is some evidence that side effects are dose-related.

Following table shows incidence of adverse effects in at least 5% of patients in study comparing **Wytensin** to placebo, at starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%) n = 102	Wytensin (%) n = 109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at starting dose of 16 mg/day in 476 patients, incidence of dry mouth was slightly higher (38%) and dizziness was slightly lower (12%), but incidence of most frequent adverse effects was similar to placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects reported during clinical trials but not clearly distinguishable from placebo effects and occurring with frequency of 3% or less: Cardiovascular—chest pain, edema, arrhythmias, palpitations. Gastrointestinal—nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort. Central nervous system—anxiety, ataxia, depression, sleep disturbances. ENT disorders—nasal congestion. Eye disorders—blurring of vision. Musculoskeletal—aches in extremities, muscle aches. Respiratory—dyspnea. Dermatologic—rash, pruritus. Urogenital—urinary frequency, disturbances of sexual function. Other—gynecomastia, taste disorders.

Drug Abuse and Dependence:
No dependence or abuse has been reported.

Overdosage:
Accidental ingestion caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two children aged one and three years. Gastric lavage and pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both. Since experience with accidental overdosage is limited, suggested treatment is mainly supportive while drug is being eliminated and until patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. Adequate airway should be maintained and, if indicated, assisted respiration instituted. No data are available on **Wytensin** dialyzability.

Dosage and Administration:
Individualize dosage. A starting dose of 4 mg b.i.d. is recommended, whether used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg/day every one to two weeks, depending on response. Maximum dose studied has been 32 mg b.i.d., but doses this high are rarely needed.

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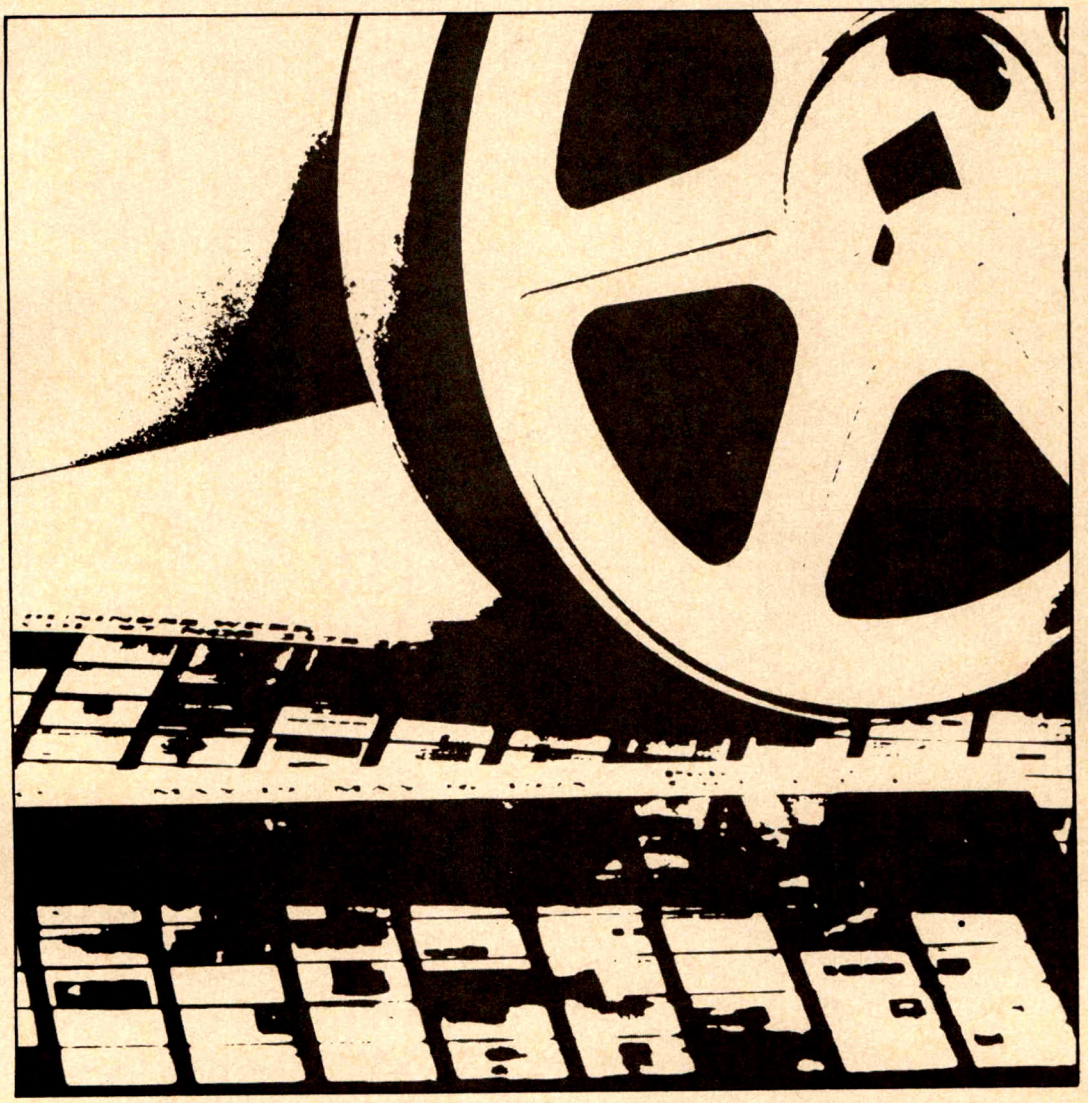

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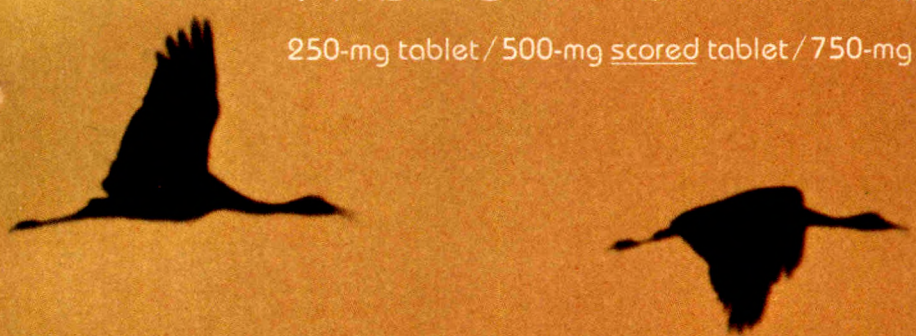

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Please see next page for brief summary of prescribing information.

Procan® SR
(procainamide hydrochloride tablets)
SUSTAINED RELEASE

Before prescribing, please see full prescribing information.
A Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: General —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

ADVERSE REACTIONS: Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED: Procan SR 250 mg (green, film-coated tablet. P-D 202) is available in bottles of 100 (N 0071-0202-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0202-40). Each sustained-release tablet contains 250 mg procainamide hydrochloride.

Procan SR 500 mg (yellow, scored, film-coated tablet. P-D 204) is available in bottles of 100 (N 0071-0204-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0204-40). Each sustained-release tablet contains 500 mg procainamide hydrochloride.

Procan SR 750 mg (orange, scored, film-coated tablet. P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

Storage—Protect from moisture. Store bottles below 86° F (30° C). Store unit-dose packages at controlled room temperature, 59°-86° F (15°-30° C).

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Prolongation of the Q-T Interval in Man During Sleep

KEVIN F. BROWNE, MD, ERIC PRYSTOWSKY, MD, JAMES J. HEGER, MD, DONALD A. CHILSON, MD, and DOUGLAS P. ZIPES, MD

Parasympathetic blockade shortens the duration of the Q-T interval and ventricular effective refractory period independent of heart rate change. Since relative parasympathetic effect increases during sleep, it was determined whether sleep was associated with a change in the Q-T interval. Fifteen patients receiving no drugs underwent 3 to 6 days of continuous electrocardiographic recordings. Tracings were sampled every 30 minutes and recorded at a paper speed of 25 mm/s. This provided 12,000 Q-T and R-R intervals that were measured. Comparison of R-R intervals that had similar durations during sleep and awake states revealed that the duration of the Q-T interval was longer during sleep in all 15 patients ($p < 0.001$). Eight patients had sufficient range of overlap of R-R intervals to compare linear regression lines of Q-T intervals recorded while awake with Q-T intervals recorded while asleep. The regression lines during sleep exhibited a mean intercept change of 38 ± 37 ms and mean slope change of −0.021 ± 0.040 ms when compared with the regression lines during the awake state. The difference in Q-T interval between awake and sleep states was 19 ± 7 ms when calculated at a heart rate of 60 beats/min. These statistical comparisons of the relationship of the Q-T interval to R-R interval indicate that the Q-T interval is longer during sleep than during the awake state at the same heart rate. Prolongation of the Q-T interval during sleep may reflect increased vagal tone or sympathetic withdrawal. These changes in repolarization may be related to the diurnal variation of some ventricular arrhythmias.

Abnormal myocardial repolarization has been linked to the development of malignant arrhythmias in patients with the prolonged Q-T interval syndrome[1–3] and in patients after acute myocardial infarction.[4,5] It is clear that heart rate, drugs, electrolytes, and autonomic tone influence the Q-T interval. In previous investigations, drugs to block 1 or both limbs of the autonomic nervous system have been administered, with either rate correction formulas[6–8] or atrial pacing[9,10] used to eliminate effects of heart rate changes. However, we were unable to find any information on the effect of heightened parasympathetic tone on Q-T interval duration in man.

From the Krannert Institute of Cardiology, the Department of Medicine, Indiana University School of Medicine, and from the Veterans Administration Medical Center, Indianapolis, Indiana. This study was supported in part by Grants HL-06308 and HL-07182 from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland; by the American Heart Association, Indiana Affiliate; by the Herman C. Krannert Fund; and by the Veterans Administration Medical Center, Indianapolis, Indiana. Manuscript received January 31, 1983; revised manuscript received March 17, 1983, accepted March 18, 1983.

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Sleep represents a naturally occurring period of increased parasympathetic tone or sympathetic tone withdrawal[11,12] and may prolong the Q-T interval independently of the slowing of heart rate. This prolongation may play an important role in the decrease in ventricular ectopy noted in some patients during sleep.[13,14] Since a significant slowing of heart rate reflecting the relatively increased parasympathetic tone occurs during sleep,[12] this change alone may prolong the Q-T interval and mask any direct autonomic effect. To permit analysis of the effect of an intervention such as sleep on the Q-T interval, we developed a new method of evaluating the measured Q-T interval duration which is independent of heart rate effects. The purpose of this study was to test the hypothesis that the duration of the Q-T interval in man is prolonged during sleep.

Methods

Fifteen subjects underwent 72 to 144 hours of continuous electrocardiographic recording. All patients met the following entrance criteria: (1) no evidence of heart disease by history, physical examination, or resting electrocardiography; (2) no medications; (3) <600 premature atrial or ventricular complexes per 24 hours; (4) P-R interval during normal sinus rhythm <0.20 second; (5) QRS duration <0.10 second; and (6) corrected Q-T interval (Bazett's formula) <0.44 second. Nine

TABLE I Comparison of Individual Awake and Asleep Regression Lines

Patient	Sex	R-R Interval Range	Slope		Intercept		Calculated Q-T Interval		Corrected Q-T Interval	
			Awake	Asleep	Awake	Asleep	Awake	Asleep	Awake	Asleep
1	M	575–1,000	0.151	0.121	277	323	428	444	460	466
2	M	650–1,000	0.168	0.093	252	333	420	426	439	454
3	M	800–1,100	0.125	0.073	257	326	382	399	390	402
4	M	900–1,150	0.140	0.093	234	304	374	397	374	394
5	M	700–1,000	0.135	0.178	297	270	432	448	459	456
7	F	750–1,050	0.103	0.102	327	349	430	451	447	466
9	M	825–1,050	0.135	0.112	255	298	390	410	398	413
12	F	825–1,050	0.111	0.134	289	295	400	429	410	432
Mean			0.134	0.113	274	312	407	423	422	435
Standard deviation			0.021	0.032	28	24	22	20	33	29

subjects had 6 and 6 subjects had three 24-hour continuous electrocardiographic recordings. Tracings approximately 7.5 seconds in duration (Fig. 1) were printed out at 25 mm/s paper speed every 30 minutes. In all, 3,400 tracings were analyzed.

Data measurement: The duration of the Q-T interval was measured using a digitizing board (HP9874A) interfaced with the Hewlett-Packard 9826 computer. Four to 8 complexes were measured from each tracing. A tracing was excluded if an ectopic complex occurred during the 7.5-second interval or if any single R-R interval varied by more than 10% of the mean R-R interval. The mean R-R and Q-T intervals were computed for each tracing from the arithmetic mean of 4 to 8 consecutive complexes and logged along with the time of day and activity (Fig. 1). The duration of each Q-T interval was measured from the beginning of the Q wave to the end of the T wave. The end of the T wave was determined by drawing a tangent to the steepest portion of the downsloping T wave. The point where the tangent intersects with the isoelectric line was used as termination of the T wave (Fig. 1).

Each hour of continuous electrocardiographic recording was coded for either awake or sleep state as determined by examining the subject's diary. A transition period was defined as the 1-hour interval after the listed bedtime and the 1-hour interval before waking time. All values from the transition period were not used in the analysis.

Consistent with a previous report[15] in 2 patients, the Q-T interval recorded while the patient was standing and supine at the same heart rate did not change.

Definitions: Tracing: one 7.5-second print-out from a continuous electrocardiographic recording. Measured Q-T and R-R interval: that interval measured directly from the arithmetic mean of 4 to 8 consecutive complexes found on one 7.5-second tracing. Calculated Q-T interval: the value of the Q-T interval obtained by solving a linear regression formula for a given R-R interval. Corrected Q-T interval: the value of the Q-T interval obtained by solving Bazett's formula for a given R-R interval.

Statistical analysis: Two-way analysis of variance[16] was performed on the Q-T interval duration with the R-R interval and sleep state as independent variables. Because the awake data were skewed toward short R-R cycle lengths and sleep data were skewed to longer cycle lengths, analysis of covariance was performed on the Q-T interval with sleep state as the independent variable and R-R interval as the covariate. In addition, a plot of Q-T versus R-R interval was made for each patient. An R-R interval range was chosen so that the number of data points for awake and sleep states present in each R-R interval increment (cell size) would be relatively uniform for each patient. A linear regression line was constructed using least squares analysis[16] for sleep and awake states for each patient (Fig. 2) and for all patients taken together. Comparison of the regression lines was performed using residual mean squares test.[16] Q-T intervals were corrected for heart rate using Bazett's formula, that is, $Q\text{-}Tc = Q\text{-}T/\sqrt{R\text{-}R \text{ interval}}$. The Q-Tc intervals for awake versus sleep states were then compared using one-way analysis of variance[16] for each patient and then as a group.

Results

Eleven men and 4 women with a mean age of 44 years were enrolled in the study. There were 3,400 tracings (Fig. 1) analyzed from the continuous electrocardiographic recordings, of which 2,020 met the measurement criteria representing over 12,000 measured R-R and Q-T intervals.

Analysis of variance: The data for each patient were plotted as shown in Figure 2. An R-R interval range was chosen to permit uniform cell size for each patient. Application of 2-way analysis of variance with R-R cycle length and sleep state as independent variables revealed that the Q-T interval was longer during the sleep state compared with the awake state in all 15 patients (<0.001). The mean R-R cycle length prolonged during sleep state in all patients (760 ± 120 ms to 920 ± 140

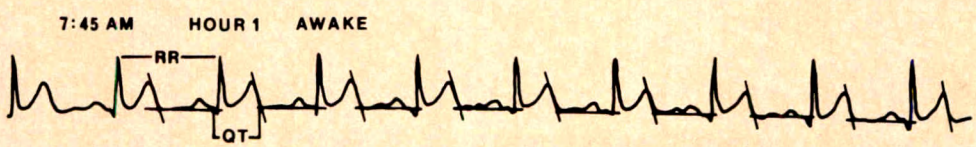

FIGURE 1. A typical tracing obtained from 1 channel of the continuous electrocardiographic recording. R-R intervals were measured from the peaks of the R waves, and the duration of the Q-T interval was measured from the onset of the QRS complex to the termination of the T wave. A tangent to the steepest portion of the downsloping T wave was constructed, and the intersection of the tangent and isoelectric line was defined as the T-wave termination.

TABLE II Comparison of Overall Awake and Asleep Regression Lines

State	Q-T Intervals (n)	Slope	Intercept	Heart Rate Range (beats/min)
Awake	1,138	0.130	277	57 to 86
Asleep	682	0.102	325	57 to 86
Simonson[23] formula	960	0.140	255*	56 to 83

* Calculated at an age of 44 years (242 + 0.3 × age).

ms). Grouping all 15 patients and performing the same analysis over an R-R interval range of 700 to 1,050 ms again showed that the Q-T interval prolonged during sleep compared with the awake state, independent of the R-R cycle length ($p < 0.001$).

Analysis of covariance: Because longer R-R cycle lengths occurred during sleep and shorter R-R cycle lengths occurred during the awake state, analysis of covariance was performed on the Q-T interval with R-R intervals covarying for each patient. Fourteen of 15 patients had significant prolongation of the Q-T interval ($p < 0.003$) during the sleep state compared with the awake state.

Linear regression analysis (Q-T = A + B × R-R interval): In 8 patients, sufficient overlap of sleep versus awake R-R intervals existed to permit construction of linear regression lines for each state over the same R-R cycle lengths. The R-R interval range, slope (B), and intercept (A) values of awake and sleep state are listed in Table I. All 8 patients had significantly different linear regression lines during sleep when compared with awake data ($p < 0.001$). In addition, the regression lines for awake state and sleep state were significantly different from the linear regression lines developed for the awake plus sleep data ($p < 0.01$). Using the regression lines in Table I, the calculated Q-T intervals for awake versus asleep state at an R-R interval of 1,000 ms were compared. The calculated Q-T interval prolonged by 19 ± 7 ms during sleep for these patients.

All patients were grouped and linear regression lines were developed for the awake and asleep state over an R-R cycle length of 700 to 1,050 ms. Table II lists the number of Q-T intervals, slope, and intercept for each state. The linear regression line developed for the awake state is similar to the linear formula of Simonson (Table II). The calculated Q-T interval prolonged 20 ms during sleep as compared with the awake state at an R-R cycle length of 1,000 ms.

Correction of the Q-T interval by Bazett's formula: The corrected Q-T interval (Q-Tc) using Bazett's formula was significantly longer in 7 of 15 patients ($p < 0.01$) during sleep than awake states when comparing all data from each patient. Two patients' Q-Tc intervals significantly shortened during sleep ($p < 0.01$) and 6 patients had no change. When the data were limited to cycle lengths compared during 2-way analysis of variance, Q-Tc was significantly longer ($p < 0.01$) during sleep in 14 of 15 patients. Pooling all 15 patients and comparing data over an R-R interval range from 700 to 1,050 ms, the Q-Tc was 424 ± 29 ms while awake and 437 ± 25 ms during sleep ($p < 0.01$). The change in the corrected Q-T interval during sleep predicted by Bazett's formula is not significantly different from the prolongation found by developing regression lines for each patient.

Discussion

Our data demonstrate that the Q-T interval prolongs during sleep independently of the change in R-R interval. The cause of this prolongation may be a change in the balance of the 2 limbs of the autonomic nervous system. It has been shown previously that during atrial pacing, loss of parasympathetic tone produced by atropine shortens the Q-T interval[10] and loss of sympathetic tone produced by propranolol either has no effect on[10] or may slightly prolong[9,10] the Q-T interval independently of change in R-R cycle length. Since all patients had sinus slowing during sleep, it may be inferred

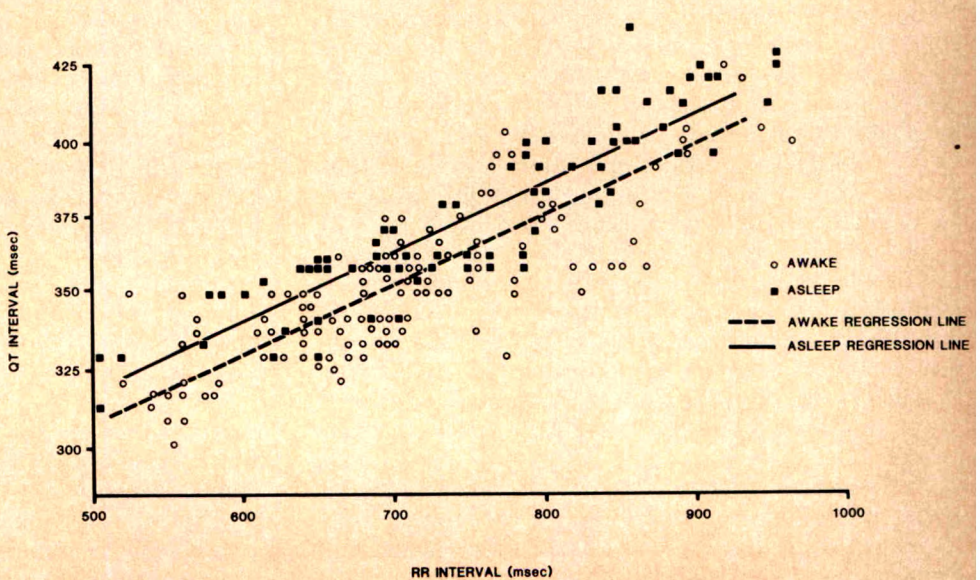

FIGURE 2. All Q-T intervals for 1 patient measured over an R-R interval range of 500 to 1,000 ms are plotted. Regression lines for awake and asleep data were constructed using least mean squares analysis.[16]

that either sympathetic withdrawal or increased parasympathetic tone or both occur during sleep. Experiments in cats have shown that slowing of heart rate during sleep is due mainly to sympathetic withdrawal.[12] Regardless of which limb of the autonomic nervous system is changing during sleep, the net result is increased parasympathetic effect. This change in autonomic balance may be responsible in part for the prolongation of the Q-T interval we have demonstrated to occur during sleep.

Other variables also may contribute to the change in the Q-T interval found in this study. The state of sleep has been shown to change relative autonomic tone.[12] During rapid eye movement sleep, there is an increase in sympathetic tone which may shorten the Q-T interval independently of heart rate change. Although we did not monitor rapid eye movement sleep, if it occurred it would have biased the sleep data to show less Q-T interval prolongation than may be present during non-rapid eye movement sleep.

The Q-T interval during the awake state may have been influenced by physical activity, meals, and activities such as smoking. Physical activity has been shown to shorten the Q-T interval but only at heart rates that would have been excluded from analysis in this study because of no comparable heart rate during sleep. Position, that is, supine compared with sitting or standing, may have influenced the results. However, it has been reported[15] that position had no effect on the Q-T interval and we found no difference in Q-T interval related to position in 2 patients.

Meals and other activities may shorten or prolong the Q-T interval an unknown amount. The data collected during these periods would comprise only a minor portion of the awake state data for any patient.

Factors other than the autonomic nervous system, such as serum potassium, calcium, pH, and body temperature, may influence sinoatrial nodal automaticity and the Q-T interval, and may vary during the sleep and awake states. It is difficult to determine the relative influence of all these factors on sinus cycle length and Q-T interval at a particular time of day or night. To complicate matters further, even at the same time of the day, the parasympathetic and sympathetic nervous system modulate sinus nodal, atrioventricular nodal, and ventricular function to different degrees.[17] This study was not designed to elucidate the mechanism for Q-T prolongation and our postulate, therefore, that prolongation of the Q-T interval at night is due mainly to heightened vagal tone remains speculative.

We[10] previously demonstrated that use of Bazett's formula to correct Q-T interval for heart rate may be invalid during changes in autonomic tone because the autonomic nervous system has both direct and heart rate-related effects on the Q-T interval. To avoid this potential error, we compared Q-T intervals measured at similar sinus cycle lengths during sleep with the awake state.

Different Q-T intervals during the awake and asleep states at similar R-R intervals can be explained by several possibilities. First, the same sinus rate at different times during a 24-hour cycle, for example while awake and asleep, does not necessarily mean the same degree of autonomic balance at each of those times. The autonomic balance affecting the sinoatrial node may remain unchanged, so the heart rate is the same, at a time when cholinergic effects on the ventricle were selectively and regionally increased or adrenergic effects decreased. Since the right stellate ganglion exerts a predominant effect on sinus rate, one could postulate constant vagal and right stellate ganglion tone (and therefore the same heart rate) associated with an increase in left stellate ganglion tone (and therefore Q-T prolongation[18]).

If similar R-R intervals while awake and asleep do indicate that the autonomic *balance* (that is, net effect) at the sinoatrial node is similar for both states, the *absolute* level of either parasympathetic or sympathetic stimulation may be different, but their net effect on the sinus node may remain unchanged. For example, during the awake state both sympathetic and parasympathetic tone may be high and during the asleep state both may be low. The net effect of the overall autonomic tone on automaticity of sinus pacemaker cells may be the same, but the effect on repolarization of ventricular muscle cells may be different. High overall autonomic tone may shorten the Q-T interval compared with low overall autonomic tone because the effects of elevated adrenergic tone may predominant over the effects of elevated cholinergic tone on ventricular repolarization. Low overall autonomic tone may result in the same *net* effect on the sinus node as high overall autonomic tone, hence the same heart rate; but during periods of low autonomic tone cholinergic effects may predominate over adrenergic effects on ventricular repolarization[19] and prolong the Q-T interval. These comments are naturally speculative and need to be tested in appropriate animal models.

The method of analysis used in this study can be applied to determine the effect that any intervention has on the duration of the Q-T interval independently of heart rate provided there is an overlap of the sinus rates before and after the intervention. For example, prolongation of the Q-T interval induced by antiarrhythmic drugs could be qualitatively and quantitatively assessed. To evaluate the effect on Q-T interval of an intervention, determination of the change in Q-T interval at multiple heart rates may give a more accurate assessment of the potential influence of heart rate. This may be important when evaluating antiarrhythmic drugs which show use dependency, that is, different effects on the action potential at different heart rates.[20] Rate correction formulas would permit comparison of Q-T intervals only at 1 corrected heart rate. Developing regression formulas allows comparison of the effect of an intervention at more than 1 heart rate. For example, sleep prolongs the Q-T interval 16, 22, and 24 ms at heart rates of 60, 70, and 80 beats/min, respectively.

Bazett's formula correctly predicted the direction of magnitude of change of the Q-T interval during sleep for the 8 patients in Table I over the listed R-R interval range. Using a wider R-R interval range of 700 to 1,050 ms, Bazett's formula predicted Q-T interval prolongation for all 15 patients as a group. By including for analysis only R-R cycle lengths in the range of 700 to 1,050 ms, correction for heart rate by Bazett's formula

was relatively accurate compared with our linear regression model in this study. Error was introduced into the formula when either faster or slower rates were corrected. It has been shown that when both Q-T interval and heart rate have large changes after an intervention, Bazett's formula may be misleading when predicting the change in Q-T interval caused by a specific intervention.[10] For those interventions in which regression analysis of the Q-T interval change compares favorably with the change found using a heart rate correction formula, it seems reasonable to apply the formula.

Sleep has been shown to be an important antiarrhythmic factor in some patients[13,21] and awakening has been related to development of arrhythmias.[22] These observations suggest that a neural mechanism operative during sleep may be responsible for the decrease in arrhythmia. In some of these patients, the decrease in arrhythmia was greater during sleep than during treatment with various antiarrhythmic drugs.[13] In our study, although the prolongation of the Q-T interval demonstrated during sleep is small, this change in the recovery of ventricular excitability may be related to the emergence or suppression of ventricular arrhythmias in some patients.

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Relation of Mode of Induction and Cycle Length of Ventricular Tachycardia: Analysis of 104 Patients

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One hundred four consecutive patients with ventricular tachycardia (VT) were examined to correlate the cycle length with the mode of initiation of VT (single, double, and triple extrastimuli and rapid pacing). Tachycardias induced with a single extrastimulus were slower (342 ± 72 ms, mean cycle length) than those induced with double (295 ± 60 ms) or triple (282 ± 56 ms) extrastimuli or rapid pacing (293 ± 40 ms). There were no differences among the last 3 groups. In 38 patients who had endocardial catheter mapping to determine the site of origin of VT, distance from stimulation site to the site of origin was estimated and correlated with mode of initiation. There was no difference in mode of initiation when the stimulation site was close (<3 cm), intermediate (3 to 5 cm), or distant (>8 cm) from the site of origin. To address the issue of distance from stimulation site to the site of origin somewhat differently, mode of initiation was correlated with site of previous myocardial infarction in 69 patients with VT initiated from the right ventricular apex. Again, mode of initiation did not differ among patients with septal, inferior, lateral, or multiple myocardial infarctions. Thus, cycle length of VT initiated with a single extrastimulus was slower than that initiated with double or triple extrastimuli or rapid pacing and the mode of initiation of VT was unrelated to site of myocardial infarction or distance between stimulation site and site of origin of VT.

Programmed electrical stimulation has been found to be a specific and sensitive technique for the diagnosis and therapy of patients with ventricular tachycardia (VT).[1–7] Although right ventricular stimulation can induce VT in most instances, left ventricular stimulation is occasionally required.[8] It has been suggested that left ventricular stimulation be used routinely in patients in whom right ventricular stimulation fails to induce VT while the patient is receiving drugs.[9] Although certain general factors influencing the ability of programmed stimulation to initiate tachycardias are known, the determinants of the mode of initiation in individual patients are incompletely understood. The present study was undertaken to determine (1) the relation of the required mode of initiation and the distance between stimulation site and VT origin, (2) the effect of site of previous myocardial infarction on mode of initiation, and (3) the relation between the method of initiation and the cycle length of VT.

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Methods

Study patients: The patient population consisted of 104 consecutive patients with inducible sustained VT during programmed ventricular stimulation. Patients in whom ventricular fibrillation or polymorphic VT causing rapid hemodynamic collapse was induced were excluded. The clinical

TABLE I Characteristics of the Study Population (n = 104)

Sex: 84 men (81%), 20 women (19%)	
Ages: 23 to 74 years (mean 57)	
Previous myocardial infarction	78 (75%)
Left ventricular aneurysm	59 (57%)
Cardiac diagnoses	
Coronary artery disease	78
Valvular disease	9
Primary electrical disease	8
Dilated cardiomyopathy	6
Postoperative tetralogy of Fallot	3

characteristics of the study population are summarized in Table I. Left ventricular endocardial catheter mapping was done in 38 patients to localize the site of origin of the VT.

Electrophysiologic study: Electrophysiologic study was performed in the postabsorptive state. Antiarrhythmic agents were discontinued for at least 5 half-lives before study in all patients. Two to 6 electrode catheters were inserted percutaneously through the femoral or brachial vein and positioned in the heart under fluoroscopic guidance. Routinely, catheters were positioned in the high right atrium, His bundle region, coronary sinus, and right ventricular apex. Our stimulation protocol has been reported previously in detail.[2,3,10]

Protocol: The protocol involved 4 stages. (1) Single and double ventricular premature extrastimuli were introduced during at least 2 paced cycle lengths (S_1-S_1 most often 600 and 400 ms) from 1 to 3 right ventricular sites. All patients were studied from the right ventricular apex. Single premature stimuli (S_2) were introduced late in diastole and moved to progressively shorter coupling intervals by 10 ms decrements until ventricular refractoriness was reached. Double premature stimuli were then introduced (S_2-S_3) with the S_1-S_2 interval 50 to 100 ms longer than the ventricular effective refractory period and the S_2-S_3 interval at twice the S_1-S_2 interval. The S_2-S_3 interval was then shortened by 10 ms decrements until S_3 reached refractoriness. The S_1-S_2 interval was then shortened by 10 ms decrements until S_3 evoked a response. This process was continued until S_2 and S_3 were refractory. Bursts of rapid ventricular pacing or triple premature ventricular depolarizations were then performed. Triple extrastimuli were given in all patients in whom double extrastimuli or rapid ventricular pacing failed to initiate VT. (2) Rapid ventricular pacing (15 to 30 seconds) to a cycle length of 250 ms was delivered from 1 right ventricular site. (3) Triple premature stimuli (S_3-S_4) were introduced in a fashion similar to that used previously for double premature stimuli with the S_1-S_2 interval 50 to 100 ms longer than the ventricular refractory period and the S_2-S_3 interval and S_3-S_4 interval 2 and 3 times the S_1-S_2 interval, respectively. (4) If VT was not initiated by the foregoing techniques, stimulation from the right ventricular mid-septum, outflow tract, and left ventricle was employed using a similar protocol.

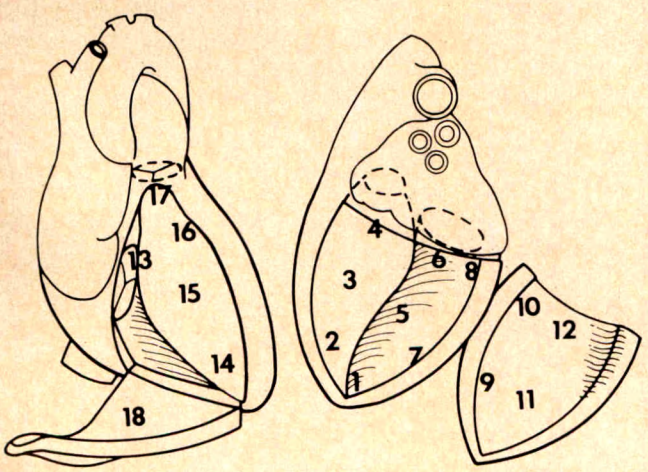

FIGURE 1. Schema of left ventricular endocardial catheter mapping sites used in our patients in the left anterior oblique projection. Site 1 represents the left ventricular apex, sites 2 to 4 are septal, sites 5 and 6 are inferior, sites 6, 8, and 10 are basal along the mitral valve ring, and sites 7, 9, 11, and 12 are on the left ventricular free wall. Sites 13 to 17 are right ventricular septal sites at the tricuspid valve, apex, mid and high septum, and outflow tract, respectively. Site 18 is the right ventricular free wall.

Stimulation was performed with a specially designed programmable stimulator (Bloom Associates, Narbeth, Pennsylvania). The stimuli were rectangular pulses 1 ms in duration delivered at twice diastolic threshold. Intracardiac electrograms were filtered at 30 to 500 Hz and simultaneously displayed with 2 to 3 surface electrocardiographic leads, usually leads I, aVF, and V_1 on a multichannel oscilloscope (Electronics for Medicine VR12 or VR16), stored on analog tape (Honeywell 5600), or later retrieved on photographic paper and simultaneously recorded with a jet-ink recorder (Elema Mingograf) at paper speeds at 100 to 200 mm/s for real-time analysis.

Endocardial catheter mapping: The catheters used for mapping included quadripolar woven dacron catheters with a 0.5 cm intraelectrode distance (USCI, Billerica, Massachusetts), and modified USCI cournand catheters with electrodes 1.5 mm apart (Wilton Webster, Los Angeles). Six right ventricular sites and 12 to 15 left ventricular sites were mapped during sinus rhythm and during VT. Each preselected site (Fig. 1) was verified by multiple plane fluoroscopy. The site of origin of the VT was defined as the site demonstrating the earliest recorded discrete or fragmented ventricular electrogram during VT using the electrode pair with a 1 cm interelectrode distance. The technique of endocardial catheter mapping has been reviewed in detail elsewhere.[4,5] In those tachycardias in which the origin was localized by catheter mapping, the distance between the site of stimulation and the site of origin of the VT was determined. If the site of origin was at the site of stimulation or at an adjacent site (on the same or opposite side of the ventricular septum), it was considered close (for example, stimulation site at site 14 and site of origin at site 2). This generally corresponded to an estimated distance of <3 cm. When the site of stimulation was ≥ 3 sites removed from the site of origin, this was considered distant and corresponded to an estimated separation of > 3 cm (for example, site of stimulation at site 14 with a site of origin at 10). When the site of stimulation was 2 sites away from the origin, it was termed intermediate and corresponded to a distance of 3 to 5 cm (for example, stimulation site 14 with a site of origin at 5). For this aspect of the study, stimulation was always performed from the right ventricular apex. Analysis of variance, chi-square, and unpaired student's *t* test were used for statistical analysis.

Results

Mode of initiation versus distance between site of origin and stimulation: In 38 patients the site of origin of VT was determined by endocardial catheter mapping. These patients were separated into 3 groups to compare the mode of initiation and the distance be

tween the site of stimulation and the site of origin of VT when the site of stimulation was close, intermediate, or distant from the stimulation site. In all cases stimulation was performed from the right ventricular apex. Of 11 patients whose VT site of origin was close to the stimulation site, 1 required a single extrastimulus, 6 required double extrastimuli, 2 required triple extrastimuli, and 2 required rapid pacing for initiation of their VT (Fig. 2). In patients in whom the distance was intermediate, 1 required a single extrastimulus, 5 required double extrastimuli, 1 required triple extrastimuli, and 1 required rapid pacing. Finally, in those patients in whom the site of origin was distant from the stimulation site, 3 required a single extrastimulus, 11 required double extrastimuli, 5 required triple extrastimuli, and none were initiated with rapid pacing. There was no difference in the stimulation protocol required to initiate VT when the site of origin was close, intermediate, or distant from the stimulation site (Fig. 2). Most patients required double extrastimuli for initiation in each of the groups.

Mode of initiation versus site of previous myocardial infarction: In 69 patients who had VT initiated from the right ventricular apex, the mode of initiation was compared with the site of previous myocardial infarction by surface electrocardiography (Fig. 3). In patients with anteroseptal myocardial infarction, 6 were induced with a single extrastimulus, 5 were induced with double extrastimuli, 7 were induced with triple extrastimuli, and 2 were induced with rapid ventricular pacing. In patients who had an inferior wall myocardial infarction, 6 were induced by a single extrastimulus, 10 were induced by double extrastimuli, 10 were initiated by triple extrastimuli, and none were initiated with rapid pacing. In patients with lateral wall myocardial infarction, 2 were induced with a single extrastimulus, 7 were induced with double extrastimuli, 2 were induced with triple extrastimuli, and none were induced with rapid ventricular pacing. In patients with multiple myocardial infarctions, 4 were induced with a single extrastimulus, 7 were induced with double extrastimuli, 1 was induced with triple extrastimuli, and none were induced with rapid ventricular pacing. No correlation was found between the site of previous myocardial infarction and the method of initiation.

Distance between site of origin and stimulation site versus cycle length of tachycardia: The cycle length of VT when the site of origin was close (mean 304 ± 69 ms), intermediate (mean 356 ± 63 ms), or distant (mean 325 ± 57 ms) from the stimulation site were not significantly different.

Mode of induction versus cycle length of VT: In the 104 patients, 126 morphologically distinct tachycardias were induced (for instance, contralateral bundle branch block pattern or difference in mean QRS axis ≥90°, Table II). The mean cycle length of VT in patients induced with a single extrastimulus was 342 ± 72 ms; in those induced with double extrastimuli, 295 ± 60 ms; in those induced with triple extrastimuli 282 ± 56 ms, and in those induced with rapid pacing, 293 ± 40 ms. The mean cycle length of VT induced with a single extrastimulus was significantly longer than that of VT induced with double or triple extrastimuli or rapid pacing. There were no significant differences among the latter 3 groups. The numbers of patients who required right ventricular outflow tract or left ventricular stimulation for initiation of VT are too small to analyze separately.

Discussion

Programmed electrical stimulation is a technique that has been demonstrated to be both sensitive and specific in replicating the laboratory clinical VT, and in predicting the success or failure of a drug regimen.[6,7,11] Until recently, most laboratories have used single and double extrastimuli and rapid ventricular pacing as their stimulation protocol.[2,12,13] Currently, triple extrastimuli also are used. It has been stated that more vigorous stimulation may be needed if there is more intervening tissue between the stimulation site and the site of origin of the VT.[14] It has even been suggested that left ventricular stimulation be used routinely in as-

Mode of Initiation	DISTANCE BETWEEN SITES OF ORIGIN AND STIMULATION		
	Close	Intermediate	Distant
Single	1	1	3
Double	6	5	11
Triple	2	1	5
Rapid Pacing	2	1	0
Total	11	8	19

FIGURE 2. Mode of initiation is compared with distance between sites of origin and stimulation in the 38 patients who underwent complete left ventricular mapping. Statistical analysis was done by R by C contingency tables (chi-square).

Mode of Initiation Right Ventricular Apex	SITE OF PREVIOUS INFARCTION			
	Septal	Inferior	Lateral	Multiple
Single	6	6	2	4
Double	5	10	7	7
Triple	7	10	2	1
Rapid Pacing	2	0	0	0
Total	20	26	11	12

FIGURE 3. Mode of initiation is compared with site of previous myocardial infarction in 69 patients whose ventricular tachycardia was initiated from the right ventricular apex. Statistical analysis was done by R by C contingency tables (chi-square).

TABLE II Mode of Initiation of Ventricular Tachycardia (VT) Compared With Cycle Length of the 126 Morphologically Distinct Tachycardias in 104 Patients

Mode of Initiation of VT	Cycle Length of VT
Single (27)	342 ± 72*
Double (55)	295 ± 60
Triple (35)	282 ± 56
Rapid pacing (9)	293 ± 40

Values are means ± standard deviation. Numbers in parentheses indicate number of morphologically distinct tachycardias initiated with each modality.
* $p < 0.05$.

sessing drug therapy in patients who are noninducible with right ventricular stimulation.[9] An unexpected finding in the study was the lack of correlation between the vigor of the stimulation protocol required to initiate VT and the distance between the site of stimulation and the site of origin. Early in the clinical experience with programmed stimulation, it was noted that VTs terminated with single extrastimuli had longer cycle lengths or were closer to the site of stimulation (usually >350 ms, isilateral ventricle), or both, than those terminated with double extrastimuli (usually <350 ms, contralateral ventricle).[2] It was thus reasoned that the amount of interevening tissue and, hence, the site of stimulation could influence the mode of initiation.

It was also observed in patients with the preexcitation syndrome that circus movement supraventricular tachycardias utilizing a left-sided Kent bundle could occasionally not be initiated from a right-sided chamber, whereas they could be easily started by left atrial stimulation.[15] Site of stimulation in this case appeared to relate both to the ease of creating unidirectional block and the ability of that area to recover excitability so that it could be reexcited. This observation was subsequently applied to stimulation techniques employed to initiate VT.[2,12] Previous studies from our laboratory[8] suggested that no clinical electrocardiographic, hemodynamic, angiographic, or electrophysiologic characteristics were able to identify the 12 of 108 patients with VT who required left ventricular stimulation for induction of their arrhythmias. Specifically, the location of previous myocardial infarction and right or left ventricular refractoriness did not separate this group from the other patients. No explanation was readily apparent to explain the failure of right ventricular stimulation in these patients.

We also have correlated the distance between the site of origin and stimulation site with the cycle lengths of the VT induced. If, by chance, VT distant from the site of stimulation was slower as a group, they would be more likely to be initiated by less vigorous stimulation techniques (that is, single premature extrastimuli). This could obscure the expected findings of a more vigorous protocol required to initiate VT at a distant site. There were, however, no differences among cycle lengths of VT induced when the site of origin was close, intermediate, or distant from the stimulation site. Although in all c our patients the data were related to induction from th right ventricular apex, in the small number of patient who required a different site of stimulation for induc tion, the distance of the stimulation site from the sit of origin of the VT did not appear to influence th number of extrastimuli required to initiate the VT c its cycle length. There are too few of such patient however, for statistical analysis.

There are obvious difficulties in estimating distanc from stimulation site to origin site. The largest potenti source of error is the difference in heart size amon patients. To overcome this difficulty, we also compare the location of previous myocardial infarction by elec trocardiogram with the mode of initiation in those pa tients in whom VT was induced from the right ver tricular apex. This site was chosen since it is reasonabl reproducible from patient to patient. These result confirmed the lack of correlation between the mode c initiation and distance from stimulation to origin see with left ventricular mapping. Patients with multipl infarctions, in whom conduction of the stimulated im pulse presumably would travel through more abnorma tissue, did not require more vigorous stimulation tech niques for the initiation of VT. Thus, no explanation immediately apparent to rationalize the discordanc between distance from site of stimulation to site of V origin and mode of initiation. It may be necessary t examine 3-dimensional propagation of wavefronts an development of local block to fully develop the questio Perhaps a narrow isthmus to the site of initial block required to initiate reentry.

Our results demonstrate that VT induced with single extrastimulus was slower than those induced wit double or triple extrastimuli or by rapid pacing. Ther was no difference among the latter 3 groups. Th suggests that in the VT initiated with a single extra stimulus, conduction may already be markedly slowe with respect to refractoriness and that additional ex trastimuli are not required to prolong conduction. Th slowed conduction could, of course, explain the longe cycle lengths of these tachycardias. The fact that drug which further prolong conduction and slow VT cyc length frequently facilitate VT induction, that is, de crease the number of extrastimuli required for initia tion, supports this hypothesis.[16] Why VT initiated wit triple extrastimuli were not more rapid than those in duced with double extrastimuli is not apparent, bu there are several plausible explanations. The effects o refractory periods may be maximized after 2 prematu ventricular depolarizations. The added extrastimu may, thus, either fail to shorten refractoriness or b contrabalanced by further prolongation in conductio in the other limb of the VT. The third possibility is tha cycle length is not related to refractoriness.

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Cardiac Arrest in Young, Ostensibly Healthy Patients: Clinical, Hemodynamic, and Electrophysiologic Findings

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This study examines the clinical, hemodynamic, and electrophysiologic findings in a unique group of 11 young (aged 15 months to 29 years) survivors of a cardiac arrest. All patients were previously in good health, and cardiac arrest was the initial manifestation of cardiac disease in all. Overt clinical and hemodynamic abnormalities were not as common as previously reported, and in some instances apparent cardiac abnormalities failed to provide a link to cardiac arrest. No patient had congenital heart disease or hypertrophic cardiomyopathy. However, during multicatheter electrophysiologic study, sustained tachyarrhythmia was reproducibly initiated in 8 of 11 patients (73%).

Young, ostensibly healthy patients who survive cardiac arrest form a diverse group. Diligent programmed intracardiac electrical stimulation may demonstrate life-threatening tachycardias in these patients. Treatment to prevent recurrence of cardiac arrest is difficult in this group of patients. However, the ability to initiate tachycardia in the electrophysiologic laboratory may be useful in the management of these patients.

Cardiac arrest in young, ostensibly healthy patients is uncommon, and to date most studies of this problem have described findings at postmortem cardiac examination of the unresuscitated victims. Previous studies have concluded that in the young cardiac arrest victim, associated cardiac disease, either congenital or acquired, is nearly always present, and an antemortem diagnosis of cardiac disease has usually been made.[1–5] In an international cooperative study of 254 cases of sudden unexpected death in victims aged 1 to 21 years, only 8 (3%) had no previous history of cardiovascular disease.[1] Postmortem examinations have identified congenital heart disease,[1] myocarditis,[1,2] dilated cardiomyopathy,[1,4] hypertrophic cardiomyopathy,[3] and intramyocardial coronary artery[5] as causes of cardiac arrest in young patients. Studies of young survivors of cardiac arrest have been limited to case reports,[6,7] and it has been difficult to develop a profile of victims of this problem. This report presents results of evaluation of 11 young survivors of cardiac arrest whose initial manifestation of cardiovascular disease was cardiac arrest.

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Methods

Patient description: During the period from January 197 to July 1982, we evaluated 11 patients (8 male, 3 female) age 15 months to 29 years (mean 18 years) who had been successfully resuscitated from out-of-hospital cardiac arres Cardiac arrest was determined to have occurred if the patien became unresponsive and required cardiopulmonary resuscitation, direct-current cardioversion, or both. In all case ventricular fibrillation (VF) (10 patients) or sustained ven tricular tachycardia (VT) (1 patient) was diagnosed b paramedical or emergency room personnel.

Clinical studies: The initial evaluation of each patien included complete history and physical examination wit special emphasis on cardiovascular and neurologic examina tion. Electrocardiography, ambulatory (minimum 48 hours or continuous surveillance bedside monitoring, and echocar diography were performed in all patients. Nine patients un derwent cardiac catheterization with coronary angiograph and ventriculography, and 7 patients had graded exercis

testing. Transient anoxic encephalopathy was common, and most patients underwent electroencephalography, cerebral computerized axial tomography, or both as part of the neurologic evaluation. All patients were considered neurologically normal within 2 weeks after cardiac arrest.

Electrophysiologic evaluation: Each patient underwent multicatheter electrophysiologic studies within 1 to 4 weeks of cardiac arrest except Patient 10, who underwent study 1 year after cardiac arrest. All cardioactive drugs were discontinued for at least 3 drug half-lives. Three or four 5Fr or 6Fr multielectrode catheters were inserted percutaneously through the femoral, antecubital, and/or subclavian veins and positioned at specific intracardiac sites (right ventricular apex, His bundle recording site, right atrium, coronary sinus) as needed. Before January 1980, we performed cardiac electrical stimulation using a stimulator limited to only 2 extrastimuli; subsequently, a stimulator capable of delivering up to 4 premature stimuli was utilized. Impulse duration was 1 to 2 ms with current strength twice diastolic pacing threshold.

Due to the development of testing techniques over time, the pacing protocol varied. However, in each patient the initial electrophysiologic assessment examined characteristics of atrioventricular and ventriculoatrial conduction. Patients found to have accessory atrioventricular connections then underwent extensive studies to evaluate both their location and electrophysiologic properties with special emphasis on analysis of ventricular cycle lengths during atrial fibrillation.[8]

Ventricular stimulation was performed in all patients. Ventricular pacing trains and extra stimuli were inserted at the right ventricular apex in all patients. For purposes of this study, sustained VT was diagnosed if a single episode resulted in ≥30 QRS complexes. The pacing protocol consisted of sequential insertion of from 1 to 4 extrastimuli after an 8 to 10 beat pacing train at cycle lengths 500 ms and then 400 ms. Each extrastimulus was progressively scanned through diastole until it no longer captured, at which point it was fixed at 20 to 30 ms beyond the point of retractoriness; the next extra stimulus was then added and scanning of diastole was repeated. This process was repeated until all 4 extrastimuli (or 2 extrastimuli for early studies) were applied. The process was terminated if sustained VT was provoked. If no arrhythmias were induced by this method, right ventricular burst pacing, consisting of asynchronous insertion of 2 back-to-back trains of 6 to 8 ventricular stimuli at progressively decreasing cycle lengths (300 to 240 ms), was performed. In Patient 9, this protocol was repeated in both the right and left ventricles before and during isoproterenol infusion (0.05 μg/kg/min).

TABLE I Clinical Features

Patient	Age (yr) & Sex	Prior Symptoms or Diagnosis	Activity at Cardiac Arrest
1	13M	Palpitations	Baseball
2	15M	. . .	Standing, talking
3	18F	Palpitations	Standing
4	$1^{3}/_{12}$F	. . .	Sleeping
5	29M	. . .	Baseball
6	27F	. . .	Bathroom floor?
7	27M	Raynaud's phenomenon	Sleeping
8	18M	. . .	Running
9	18M	Palpitations	Wrestling
10	12M	. . .	Running
11	21M	. . .	Standing

Treatment: In 3 of the first 4 patients, sustained tachyarrhythmias could not be induced; their treatment was empirical. This usually consisted of propranolol alone or in combination with phenytoin. In subsequent patients, all of whom had inducible tachycardia, serial electrophysiologic studies were performed in the presence of an antiarrhythmic treatment regimen with a view toward establishing a treatment program which prevented induction of sustained tachycardia. In some patients, it was not possible to achieve this goal with available antiarrhythmic drugs or surgery. Consequently, investigational antiarrhythmic drugs (bethanidine sulfate, amiodarone) were evaluated. We used amiodarone as the treatment of last resort, and for this drug, electrophysiologic testing of efficacy was not performed.[9]

After hospital discharge, patients were returned to the care of their referring physician. The patients were referred from a wide geographic region and personal follow-up was not possible in all cases. Therefore, for some patients, follow-up information was updated quarterly based upon telephone contact with either the patient or the patient's physician.

Results

Table I summarizes the clinical features of the 11 patients. Table II summarizes the findings of their cardiovascular evaluation, and Table III summarizes the findings of their electrophysiologic evaluation and treatment.

Five patients were engaged in or recovering from mild to moderate exercise at the time of cardiac arrest. The remaining 6 were relatively sedentary; 2 patients were sleeping at the time of cardiac arrest (Table I). Before

TABLE II Cardiovascular Evaluation

Patient	ECG	Monitoring	Echocardiogram	Treadmill	Coronary Angiograms	Ventriculograms		LVEDP (mm Hg)	Diagnosis
						Right	Left		
1	Normal	Normal	Normal	Normal	Normal	. . .	Normal	8	. . .
2	Normal	Normal	Normal	Normal	. . .	. . .	. . .	. . .	. . .
3	Normal	VPC	Normal	Ectopy	Normal	. . .	Normal	11	. . .
4	Normal	VT	Normal	. . .	. . .	. . .	. . .	. . .	Myocarditis
5	Normal	Normal	Normal	Normal	Normal	. . .	Normal	8	. . .
6	P-R = 0.11	VT	LV Dysfunction	. . .	Normal	. . .	Large	11	DC
7	Normal	Normal	Normal	. . .	Normal	. . .	Normal	8	Scleroderma?
8	WPW Syndrome	Normal	Normal	. . .	Normal	. . .	Normal	9	. . .
9	NSSTTWC	Normal	TVP	SVT (280/min)	Normal	TVP	Normal	8	TVP
10	Normal	Normal	Normal	ST↓	Bridge	Normal	Normal	26	Bridge, RC
11	Normal	VPC	LV Dysfunction	Normal	Normal	Normal	Large	9	DC

DC = dilated cardiomyopathy; ECG = electrocardiogram; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; NSSTTWC = nonspecific ST-T–wave changes; RC = restrictive cardiomyopathy; SVT = supraventricular tachycardia; TVP = tricuspid valve prolapse; VPC = ventricular premature contraction; VT = ventricular tachycardia.

TABLE III Results

Pt	Sustained Tachycardia	Treatment	Follow-Up (months)	Recurrence
1	VT (CL 200 ms)	Propranolol	12	+ (sudden death)
2	0	Propranolol	8	+ (sudden death)
3	0	Propranolol, DPH	41	+ (VT)
4	0	Quinidine,	1 wk	+ (VT)
		propranolol,	1	+ (VT)
		DPH	26	0
5	VT (CL250 ms)	Procainamide	25	0
6	VT (CL200 ms)	Quinidine	18	+ (sudden death)
7	VT (CL220 ms)	Quinidine,	7	+ (VT)
		amiodarone	8	0
8	Antidromic-AF	Surgery-PSAC	14	0
9	SVT (CL220 ms)	Surgery-LLAC	8	0
10	VT (CL235 ms)	Surgery-bridge,	23	+ (VF)
		amiodarone	1	0
11	VT (CL170 ms)	Amiodarone	6	0

AF = atrial fibrillation; CL = cycle length; DPH = diphenylhydantoin; LLAC = left lateral accessory connection; PSAC = posterior septal accessory connection; Pt = patient; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia; + = present; 0 = absent.

cardiac arrest, all patients were free of cardiovascular symptoms except for Patients 1, 3, and 9, who had had occasional palpitations which had been present for 1 month to 3 years and had not required medical attention. Patient 7 had a 4-year history of mild symptoms of Raynaud's phenomenon. No other patient had any recognized chronic medical problem, and none were taking any chronic medication at the time of cardiac arrest. There were no other cases of cardiac arrest in first order relatives.

Cardiovascular evaluation: In 8 patients, standard electrocardiograms were normal (Table II). One patient had classic electrocardiographic features of Wolff-Parkinson-White syndrome, 1 patient had a short P-R interval (0.11 second), and 1 patient had nonspecific ST-T–wave changes. The Q-T interval was normal in all patients. Ambulatory or bedside monitoring showed no abnormalities in 7 patients. VT was observed in Patients 4 and 6; Patient 6 required direct-current cardioversion of spontaneously occurring VT during hospital admission. In this patient, VT initiated during electrophysiologic study was identical to the spontaneous episode. Multimorphic ventricular premature contractions were seen in Patients 3 and 11.

Single and 2-dimensional echocardiograms were normal in 8 of 11 patients. A dilated left ventricle with poor wall motion was present in Patients 6 and 11. Prolapse of the tricuspid valve associated with auscultatory findings of mild tricuspid regurgitation was seen in Patient 9.

Treadmill exercise testing was normal in 4 of 7 patients (Bruce protocol). Baseline ventricular ectopy increased with exercise in Patient 3, and S-T segment depression developed in Patient 10. Supraventricular tachycardia (cycle length 220 ms) associated with S-T segment depression and hypotension developed in Patient 9 (Fig. 1).

Cardiac catheterization with angiography was performed in 9 patients. Intracardiac pressure measurements were normal in 8 of 9 patients, but Patient 10 had a markedly elevated left ventricular end-diastolic pressure. Coronary angiography was normal in 8 patients, but in Patient 10 external systolic compression of the left anterior descending coronary artery by myocardial bridges (approximately 75% reduction in coronary artery diameter) was present. Ventriculograms were normal in 6 of 9 patients. A right ventriculogram confirmed the echocardiographic impression of mild tricuspid valve prolapse and regurgitation in Patient 9. Patients 6 and 11 had large dilated left ventricles with ejection fractions of 34 and 39%. Patient 7 had mild left ventricular dysfunction with an ejection fraction of 51%.

Cardiovascular diagnosis: After cardiac arrest, a cardiovascular diagnosis was made in 6 patients (Table II). Based on an increase in titers to Coxsackie B-2 virus

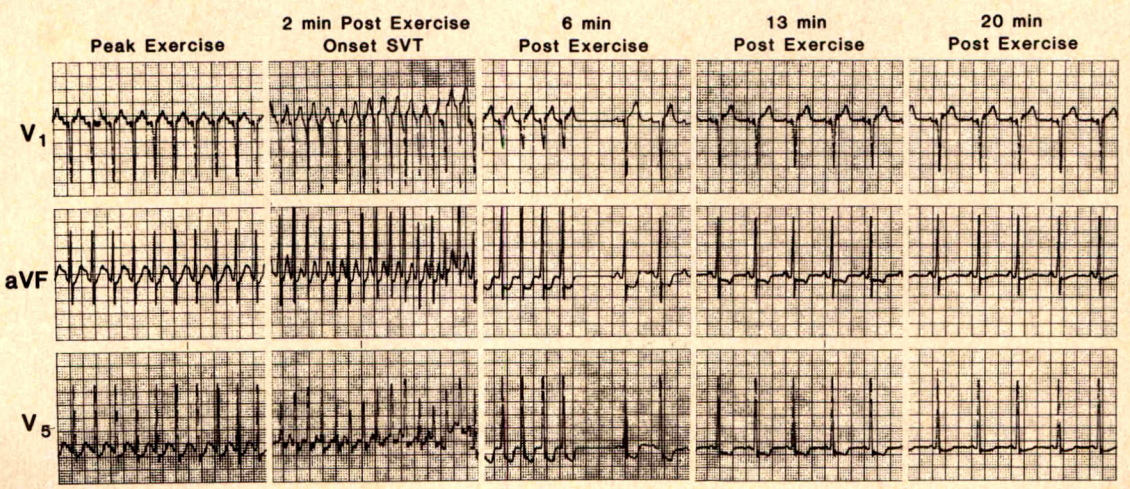

FIGURE 1. Spontaneous onset of orthodromic reciprocating tachycardia during treadmill exercise in Patient 9. In this instance, tachycardia began 2 minutes after exercise. Initially, the cycle length of the tachycardia is short (220 ms), but it gradually lengthens and tachycardia spontaneously terminates in about 4 minutes. The patient felt compelled to sit during tachycardia. While sitting, his peak systolic blood pressure was 100 mm Hg. Transient S-T segment abnormalities developed during exercise but returned to normal within 11 minutes. SVT = supraventricular tachycardia.

Patient 4 was thought to have viral myocarditis. Patients 6, 7, and 11 had dilated cardiomyopathy; in Patient 7, a diagnosis of collagen vascular disease, probably scleroderma, was suspected. Patient 9 had tricuspid valve prolapse. Patient 10 had myocardial bridges and a restrictive cardiomyopathy. No patient was found to have congenital heart disease, hypertrophic cardiomyopathy, or arrhythmogenic right ventricular dysplasia.[10]

Electrophysiologic evaluation: Rapid sustained tachycardia was initiated in 8 patients (73%) and in 3 patients either no arrhythmia or VT of <4 beats was observed. The 3 patients without inducible arrhythmia were studied early in our experience when the stimulation protocol was limited to 2 extrastimuli. VF did not occur during catheter study in any patient, presumably due to prompt cardioversion of hemodynamically deleterious arrhythmias.

Accessory atrioventricular connections were demonstrated in 2 patients. Patient 8 had a posterior septal accessory connection with only anterograde conduction, which participated in antidromic tachycardia that degenerated to atrial fibrillation. Isoproterenol administration during atrial fibrillation resulted in R-R intervals as short as 180 ms.[7] Patient 9 had a left lateral accessory connection which conducted only in the retrograde direction; ventricular preexcitation was never seen. This accessory connection participated in orthodromic tachycardia (cycle length 220 to 290 ms) which was associated with hypotension at short cycle lengths (peak systolic blood pressure as low as 60 mm Hg in supine position). To exclude a propensity to VT, this patient also underwent stimulation of both ventricles with 4 sequential extrastimuli before and during isoproterenol infusion. VT was not induced.

In 6 patients, rapid, sustained VT was initiated. Profound hypotension associated with induced VT necessitated direct-current cardioversion in all 6 patients on 2 or more occasions. In each patient, characteristics of VT were similar to previously initiated episodes. In Patient 1 this was accomplished by rapid atrial pacing. In Patients 5, 6, 7, 10, and 11 this was accomplished by sequential insertion of 3 or 4 extrastimuli from the apex of the right ventricle (Fig. 2).

Treatment: Recurrences of cardiac arrest (3 of 11) or symptomatic VT (3 of 11) were common, even when antiarrhythmic drugs were employed. Table III summarizes the therapy for all patients. A number of factors played a role in selection of therapy in individual patients. Early in our experience, serial electrophysiologic drug testing was not part of our routine management of cardiac arrest survivors. In the first 4 patients, we relied on empiric treatment usually with propranolol, alone or combined with phenytoin. However, all 4 patients treated with these empiric regimens had recurrences and 2 died.

One month after cardiac arrest, Patient 10 underwent surgery for release of myocardial bridges. One year after surgery, coronary and left ventricular angiography were normal; however, hemodynamic evidence of restrictive cardiomyopathy remained. Electrophysiologic testing, which was previously deferred because of concerns that ventricular ischemia was present, was performed 1 year after surgery. This patient withdrew from testing before a satisfactory treatment regimen could be found, and he was discharged on no therapy. However, 23 months after his initial presentation, he had a second cardiac arrest.

Both Patients 8 and 9 underwent surgery for ablation of accessory connections, and they have done well in follow-up of 8 and 14 months. Serial electrophysiologic testing of antiarrhythmic drug effects were performed in Patients 5, 6, 7, 10, and 11. When VT could no longer be induced by electrical stimulation, therapy was considered adequate. In Patients 6 and 7, quinidine sulfate prevented the initiation of VT, but both patients had

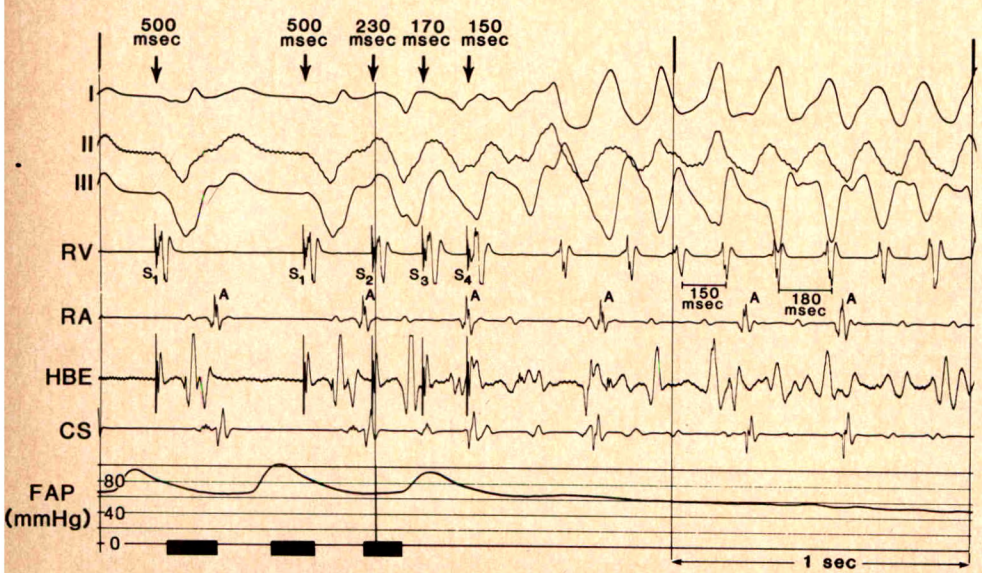

FIGURE 2. Initiation of rapid, sustained ventricular tachycardia in Patient 11 with 3 sequential extrastimuli (S_2, S_3, S_4) after a basic drive (S_1) at 500 ms. Direct-current cardioversion was required to terminate this episode of ventricular tachycardia. I, II, III = standard surface electrocardiograms; CS = electrograms from coronary sinus; FAP = femoral artery pressure; HBE = His bundle electrogram; RA = right atrial electrogram; RV = right ventricular electrogram.

a recurrence. Patient 6 died; Patient 7 was treated with amiodarone. In Patients 10 and 11, antiarrhythmic drugs with acceptable adverse effects that prevented the initiation of VT were not found; they were treated with amiodarone. Electrophysiologic testing of amiodarone was not performed in Patients 7, 10, and 11. All 3 patients have done well with amiodarone during short follow-up (1 to 8 months).

Postmortem examination: Patients 2 and 6 underwent postmortem cardiac examination by a medical examiner. No structural defects were found in Patient 2. Patient 6 had typical findings of dilated cardiomyopathy.

Discussion

Young, ostensibly healthy patients who survive cardiac arrest form a diverse group. The major finding of our study is that a rapid tachyarrhythmia could be induced in most (73%) of these patients. It is presumed that a spontaneously occurring tachyarrhythmia with deleterious hemodynamic consequences, similar to that initiated during electrophysiologic study, was the basis for cardiac arrest. This possibility was confirmed in 1 case.

The percentage of our patients with inducible arrhythmia compares well with results of previously reported studies of patients with[11] and without[12] coronary artery disease. The use of electrophysiologic testing as a guide to selection of therapy to prevent recurrences is not as encouraging as reported in older survivors of cardiac arrest.[11,12] One explanation for this apparent disparity could be the small number of patients we studied. Alternatively, cardiac arrest in some patients may represent an early manifestation of a progressive disease. Two patients illustrate this point well. Cardiac arrest was the initial manifestation of disease in Patient 6, but during evaluation, dilated cardiomyopathy was found. Progression of disease was suggested by symptoms of heart failure which appeared 1 year later. A fatal recurrence of cardiac arrest occurred 18 months after initiation of therapy which had prevented induction of VT. Patient 7 had a nonfatal recurrence of VT while taking therapy which had prevented induction of VT. Concomitantly, further progression of collagen-vascular disease, probably scleroderma, was noted with pulmonary and renal involvement. If other patients with recurrences live long enough, they may have additiona manifestation of disease. This seems especially true fo patients with cardiomyopathy.

Our study differs from those previously reporte since we studied survivors. As in previous studies, w found that associated cardiovascular abnormalities wer common, but in only 5 of 11 patients were they likely t have been etiologic in cardiac arrest (myocarditis 1 cardiomyopathy 4). However, findings in other patient suggest that there may not always be a link between a overt cardiac abnormality and cardiac arrest. For ex ample, Patient 9 was found to have tricuspid valv prolapse and a left lateral accessory connection. Su praventricular tachycardia was the only arrhythmi induced even though aggressive stimulation of bot ventricles, before and during isoproterenol infusion, wa performed. If this patient had not been resuscitate from cardiac arrest, tricuspid valve abnormalities ma have been noted at autopsy and might have been con sidered etiologic in the patient's cardiac arrest.

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Value of the Ajmaline-Procainamide Test to Predict the Effect of Long-Term Oral Amiodarone on the Anterograde Effective Refractory Period of the Accessory Pathway in the Wolff-Parkinson-White Syndrome

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In patients with the Wolff-Parkinson-White syndrome, intravenous ajmaline (50 mg administered over 3 minutes) or procainamide (10 mg/kg body weight administered over 10 minutes) is helpful in defining the duration of the anterograde effective refractory period of the accessory pathway. In this study the value of the ajmaline-procainamide test to predict the effects on the anterograde effective refractory period of the accessory pathway of long-term oral amiodarone were assessed. Thirty-six patients with the Wolff-Parkinson-White syndrome were studied. Twenty-four (Group A) had a negative result of the ajmaline-procainamide test and a mean duration of the anterograde effective refractory period of the accessory pathway of 237 ± 24 ms. Twelve (Group B) had a positive result in the ajmaline-procainamide test (disappearance of preexcitation during sinus rhythm after administration of ajmaline and procainamide) and a duration of the anterograde effective refractory period of the accessory pathway of 284 ± 25 ms ($p < 0.05$ versus values in Group A). Amiodarone prolonged the anterograde effective refractory period of the accessory pathway by 53 ± 35 ms in patients in Group A to 290 ± 37 ms ($p < 0.001$) and by 100 ± 85 ms in patients in Group B to 384 ± 94 ms ($p < 0.001$). The difference in mean increase between both groups was not significant. In most patients (83%) in Group A amiodarone prolonged the anterograde effective refractory period of the accessory pathway to 260 to 330 ms. However, in most patients (83%) in Group B, amiodarone prolonged the anterograde effective refractory period of the accessory pathway to ≥330 ms ($p < 0.01$). Thus, an ajmaline-procainamide test is of value in predicting the results of oral amiodarone on the anterograde effective refractory period of the accessory pathway.

In patients with the Wolff-Parkinson-White (WPW) syndrome, the intravenous administration of 50 mg of ajmaline over 3 minutes or 10 mg/kg body weight of procainamide over 10 minutes during sinus rhythm gives information about the duration of the anterograde effective refractory period of the accessory pathway. In most patients with the WPW syndrome with a duration of the anterograde effective refractory period of the accessory pathway ≥270 ms, both ajmaline[1] and procainamide[2] block anterograde conduction over the accessory pathway during sinus rhythm (a positive test). In most patients in whom the anterograde effective refractory period of the accessory pathway is <270 ms, ajmaline and procainamide fail to block anterograde conduction over the accessory pathway during sinus rhythm (a negative test).[1,2] Ajmaline is a class I antiarrhythmic agent not available in the United States. We have previously shown a good correlation between the effects of ajmaline and procainamide to block anterograde conduction over the accessory pathway in patients with the WPW syndrome.[2] Roughly 10 mg of ajmaline is equivalent to 100 mg of procainamide. Amiodarone is now being evaluated as an antiarrhythmic agent in the United States. Several studies have shown that it is of value in preventing both supraventricular and ven-

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tricular arrhythmias.[3–9] In patients with WPW syndrome, amiodarone prolongs the anterograde effective refractory period of the accessory pathway more than other antiarrhythmic agents such as procainamide, ajmaline, and quinidine.[10] At present accurate assessment of the effect of an antiarrhythmic drug on the length of the anterograde effective refractory period of the accessory pathway in patients with the WPW syndrome requires an invasive electrophysiologic investigation.

In this study we evaluated the value of the ajmaline-procainamide test in predicting the effects of oral amiodarone on the duration of the anterograde effective refractory period of the accessory pathway. We wanted to know to what extent oral amiodarone was able to lengthen the anterograde effective refractory period of the accessory pathway in patients with both positive and negative results of the ajmaline-procainamide test. The results of such a study could be of value in providing noninvasive information about the effect of amiodarone on the anterograde effective refractory period of the accessory pathway in patients with the WPW syndrome.

Methods

Patients: Thirty-six patients (28 male and 8 female) with the WPW syndrome were retrospectively studied. Their ages ranged from 16 to 62 years. Four patients had a right-sided, 6 a septal, and 26 a left-sided accessory pathway. Patients were classified into 2 groups according to the results of the ajmaline and procainamide tests, which were performed as previously described.[1,2] Twenty-four patients had a negative ajmaline test result (Group A) and 12 patients a positive test result (Group B). Eleven patients in Group A and 7 in Group B also had a procainamide test performed, with results identical to those of the ajmaline test.

Twenty-four to 48 hours after the last test (ajmaline or procainamide), an electrophysiologic study was performed to determine the duration of the anterograde effective refractory period of the accessory pathway. The extrastimulus technique was used during atrial stimulation at at least 3 different basic cycle lengths of pacing, usually 600, 500, and 430 ms. The anterograde effective refractory period of the accessory pathway was defined as the longest A_1-A_2 interval not followed by anterograde conduction over the accessory pathway. The shortest measured anterograde effective refractory period of the accessory pathway at any cycle length of pacing from the atrial site closest to the atrial end of the accessory pathway was used. Patients were not included in this study when atrial refractoriness prevented accurate measurement of the duration of the anterograde effective refractory period of the accessory pathway during the control or repeat study on oral amiodarone. After the control study, patients were given amiodarone orally starting at a dose of 600 mg/day for 7 days followed by 200 mg/day for an additional 3 to 5 weeks. The total oral dose of amiodarone at the time of examination varied individually from 8,400 to 11,200 mg. During reexamination the same protocol was followed as during the initial electrophysiologic examination. The shortest value of the anterograde effective refractory period of the accessory pathway was used for analysis. Plasma levels of ajmaline, procainamide, and amiodarone were not determined. Statistical analysis was performed using the paired and unpaired Student's t test, and the chi-square test.

Results

A summary of the duration of the anterograde ef fective refractory period of the accessory pathway befor and after administration of amiodarone is shown i Table I. In patients in Group A (with negative result of the ajmaline-procainamide test), the mean duratio of the anterograde effective refractory period of th accessory pathway before administration of amiodaron was 237 ± 24 ms. This value was significantly differen from the duration of the anterograde effective refractor period of the accessory pathway in patients in Group I (290 ± 37 ms) ($p < 0.05$). One patient (Patient 20) i Group A had an anterograde effective refractory perio of the accessory pathway >270 ms (290 ms). One patien (Patient 35) in Group B had an anterograde effectiv refractory period of the accessory pathway <270 m (230 ms).

Amiodarone prolonged the duration of the antero grade effective refractory period of the accessor

TABLE I Duration (ms) of Anterograde Effective Refractory Period of the Accessory Pathway Before and During Oral Administration of Amiodarone in the 36 Patients Studied

	Amiodarone		
Patient	Before	During	Increase
Group A (Negative Ajmaline-Procainamide Test)			
1	245	270	25
2	245	310	65
3	260	285	25
4	260	295	35
5	240	300	60
6	230	290	60
7	250	400	150
8	240	270	30
9	200	220	20
10	230	320	90
11	240	260	20
12	240	300	60
13	200	260	60
14	250	290	40
15	260	270	10
16	220	280	60
17	240	310	70
18	250	290	40
19	240	290	50
20	290	360	70
21	260	260	0
22	210	300	90
23	180	300	120
24	210	230	20
Mean ± SD	237 ± 24	290 ± 37	53 ± 35
Group B (Positive Ajmaline-Procainamide Test)			
25	270	450	180
26	300	350	50
27	270	400	130
28	310	500	190
29	280	350	70
30	290	340	50
31	270	280	10
32	270	270	0
33	330	400	70
34	300	340	40
35	230	330	100
36	290	600	310
Mean ± SD	284 ± 25	384 ± 95	100 ± 85

SD = standard deviation.

pathway in both groups: in Group A by a mean of 53 ± 35 ms, and in Group B by a mean of 100 ± 85 ms. These results were statistically significant ($p < 0.01$ in both Group A and Group B versus values in control study). In one patient (Patient 21) in Group A and 1 (Patient 32) in Group B, amiodarone did not alter the duration of the anterograde effective refractory period of the accessory pathway. The mean increase in the anterograde effective refractory period of the accessory pathway in patients in Group B was greater than in those in Group A. However, the difference in mean increase was not significant ($p > 0.05$). When individual data were analyzed, it was observed that in 10 (83%) of 12 patients in Group B, amiodarone prolonged the anterograde effective refractory period of the accessory pathway to a value ≥330 ms; in 5 of these 10 patients it was ≥400 ms. In patients in Group A a duration of the anterograde effective refractory period of the accessory pathway ≥330 ms after administration of amiodarone was obtained only in Patients 7 and 20 (400 and 360 ms, respectively). In 20 of the remaining 22 patients the anterograde effective refractory period of the accessory pathway was 260 to 320 ms, and in the remaining 2 patients it was 220 and 230 ms. In this group, 20 (83%) of 24 patients had an anterograde effective refractory period of the accessory pathway of 260 to 330 ms during administration of amiodarone ($p < 0.01$ versus values in Group A).

Discussion

In this study patients with the WPW syndrome were classified into 2 groups on the basis of the results of the ajmaline-procainamide test. The duration of the anterograde effective refractory period of the accessory pathway as shown previously was significantly different in the 2 groups during the control study.[1,2] Amiodarone brought the anterograde effective refractory period of the accessory pathway to a duration of 260 to 330 ms in the majority of patients (83%) in Group A, and to a duration ≥330 ms in 83% of patients in Group B. We and others[11–13] found a relation between the duration of the anterograde refractory period of the accessory pathway in the WPW syndrome and the shortest preexcitated R-R interval during atrial fibrillation. One might assume therefore that in a majority of Group A patients (83%), the shortest R-R interval during atrial fibrillation will not be <260 ms during amiodarone administration (corresponding to a ventricular rate of 240 beats/min). In 83% of Group B patients the shortest R-R interval will not be <330 ms (corresponding to a ventricular rate of 170 beats/min) during administration of amiodarone. In our patients, however, atrial fibrillation was not systematically initiated during the study before and after administration of amiodarone, and these considerations should be made with caution.

The results of our study show that an ajmaline-procainamide test performed before antiarrhythmic therapy is helpful in predicting the results of oral administration of amiodarone and will help to avoid a repeat electrophysiologic investigation. We recently showed that beta-adrenergic stimulation shortens the duration of the effective refractory period of the accessory pathway in patients with the WPW syndrome.[14] The results of that study indicate that the properties of the accessory pathway are dynamic, and they change with changes in autonomic tone. At present the behavior of the properties of the accessory pathway with time are unknown, and it is possible that they are not stable. The results of this study, therefore, have to be considered with caution in light of these observations.

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Evaluation of Metoprolol in Suppressing Complex Ventricular Arrhythmias

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This study documents the extent of suppression of premature ventricular beats which can be achieved with metoprolol, a semiselective beta-adrenergic blocking agent, at doses of 100 to 200 mg daily, utilizing a single-blind placebo-controlled 10-day protocol with continuous ambulatory electrocardiographic recording of 20 patients with cardiac disease and complex ventricular arrhythmias. Metoprolol (200 mg/day) resulted in suppression of 60% of total premature ventricular beats, with couplets (pairs) and ventricular tachycardia decreased 84% and 94%, respectively (all $p < 0.01$). Exercise-induced premature ventricular beats, especially ventricular tachycardia, were effectively suppressed. The peak plasma metoprolol level to achieve these results was 72 ± 34 ng/ml (mean ± 1 standard deviation). At this plasma concentration, the mean 24-hour heart rate during normal activity was reduced from 78 ± 8 beats/min (placebo) to 62 ± 4 (metoprolol 200 mg/day)($p < 0.001$). Beta blockade also was demonstrated by a 20% reduction in heart rate during maximal Bruce exercise testing with metoprolol 200 mg/day. Although resting left ventricular function was not affected by metoprolol, pulmonary function tests show a statistically significant decrease in forced vital capacity, forced expiratory volume in 1 second, and forced expiratory flow rates (25-75) reversible with a beta-2 agonist.

Ventricular rhythm disturbances have prognostic significance in identifying an increased risk for sudden cardiac death in patients after myocardial infarction.[1,2] Beta-adrenergic blocking agents are efficacious in suppressing ventricular arrhythmias, especially in specific clinical settings including catecholamine excess, digitalis toxicity, mitral valve prolapse, and those induced by exercise.[3–6] Importantly, in numerous prospective placebo-controlled randomized clinical trials of beta-blockers in patients after myocardial infarction, cardiac mortality and sudden cardiac death have been reduced. Propranolol, timolol, and metoprolol have achieved the most significant reduction in mortality and sudden death in these large clinical trials.[7–9] Although a reduction in mortality and sudden death has been documented, it has not been demonstrated that this reduction is due to suppression of ventricular arrhythmias.

Despite a substantial experience with beta-blockers the ventricular antiarrhythmic efficacy of metoprolol is poorly documented. Since the semiselective properties of this beta-blocker may be beneficial to patients with asthma or obstructive lung disease, this study was designed to assess the effect of metoprolol in suppressing complex ventricular arrhythmias, with concomitant measurement of left ventricular function, pulmonary function, and correlation with plasma metoprolol levels.

Methods

The study population consisted of 20 patients (10 male, 10 female; mean age 57 ± 8 years) with screening 24-hour ambulatory electrocardiograms demonstrating complex ventricular rhythm disturbances (frequent premature ventricular beats [PVB] ≥30 per hour, couplets, ventricular tachycardia [VT]). All 20 patients had documented cardiac disease: 15

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patients had coronary artery disease documented by previous myocardial infarction, coronary arteriography or both; 2 patients had hypertensive heart disease; 3 patients had cardiomyopathy. All antiarrhythmic medications except digitalis were discontinued at least 72 hours before the study.

The study design consisted of a 10-day placebo-controlled single-blind protocol (3 days of placebo, 3 days of metoprolol 25 mg orally 4 times a day, 4 days of metoprolol 50 mg orally 4 times a day) with continuous 24-hour ambulatory electrocardiographic recordings. These were recorded on the Avionics® 445 A 2-channel system (Irvine, California) and analysis was performed on an Avionics 668 scanner. Tapes were analyzed by 2 independent investigators. Test tapes in our laboratory show a reproducibility of 92, 93, and 95% for total counts of PVB, couplets, and VT, respectively.

Ventricular arrhythmias, as well as heart rates during normal activity, were quantitated hourly during the entire 10-day study. Symptom-limited exercise testing was performed with placebo and metoprolol (200 mg/day) utilizing the standard Bruce protocol with quantitation of ventricular arrhythmias during exercise and recovery periods. Two-dimensional echocardiographic assessment of left ventricular function was performed during placebo and metoprolol dosing on an ATL® (Bellville, Washington) mechanical sector scanner and the left ventricular ejection fraction was calculated by a method previously reported from this laboratory.[10] Sector scans performed during placebo dosing on at least 2 consecutive days demonstrated a reproducibility of the left ventricular ejection fraction of ±3%.

Pulmonary function testing was performed during placebo, then 3 times during metoprolol dosing (2 hours after the first 25 mg dose, day 3 of 25 mg 4 times daily, 2 hours after first 50 mg dose).

Spirometry was performed on an Ohio® 850 rolling-seal spirometer (Madisonville, Wisconsin) utilizing a Collins Eagle® microprocessor (Braintree, Massachusetts). Forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) were selected from the best of ≥3 forced expiratory maneuvers. The mid-maximal expiratory flow rate (FEF [25-75]) was selected from the "curve" with the best total of FVC and FEV_1. Functional residual capacity and airway resistance were determined with an Ohio variable-pressure body plethysmograph. Total lung capacity was calculated from the functional residual capacity and the inspiratory capacity during a slow vital capacity maneuver. Spirometry and plethysmography were repeated 15 minutes after metaproterenol (1.5 mg) aerosolized inhalation. Data before and after bronchodilators were expressed from norms described by Morris,[11] Goldman,[12] Boren,[13] and their co-workers. Arterial blood gases were also obtained during placebo and metoprolol dosing.

• Metoprolol plasma samples were obtained during placebo administration, and once during low- and high-dose metoprolol with samples obtained 2 hours after each dose. Additionally, a 5-hour postdose sample was taken during high-dose metoprolol therapy. All plasma samples were obtained after at least 5 doses of metoprolol at each dose range to insure a steady state at the sampling time. Quantitation of metoprolol in human plasma was performed by fluorometry after high-pressure liquid chromatographic separation. Pronethalol was used as an internal standard. Known amounts of metoprolol ranging from 5 to 1,000 ng/ml were added to plasma samples obtained from persons taking no drugs; these samples were analyzed concurrently with those from patients taking metoprolol. A standard curve for metoprolol was then constructed by linear regression plot of metoprolol/pronethalol peak height ratio versus drug concentration in the spiked samples. Metoprolol concentration in the sample patient plasma was then calculated from the regression line by the formula $Y = mx + b$, where Y is the peak height ratio, m is the slope of the regression line, x is the metoprolol concentration, and b is the Y-intercept. This method allows detection of as little as 10 ng/ml of metoprolol with intraassay and interassay coefficients of variation of 5.4% and 8.3%, respectively. Commonly used cardiovascular drugs do not interfere with this assay.

Statistical analysis was performed with the *t* statistic for paired data. The Wilcoxon signed ranks test was used for data that were not normally distributed.

TABLE I Premature Ventricular Beats (PVB): Placebo Versus Low- and High-Dose Metoprolol

Patient	3-Day Placebo: Mean PVB/24 hours	3-Day Metoprolol (100 mg/day): Mean PVB/24 hours	4-Day Metoprolol (200 mg/day): Mean PVB/24 hours
1	22,160	19,794	8,218
2	1,078	341	245
3	5,443	74	11
4	6,654	124	56
5	22,205	11,836	4,306
6	25,904	23,138	11,479
7	10,357	8,305	5,085
8	3,560	1,651	271
9	18,556	3,521	2,330
10	2,604	1,876	202
11	1,840	282	285
12	10,905	4,644	4,045
13	7,123	5,708	3,397
14	7,214	8,754	5,132
15	16,400	15,105	13,400
16	2,783	3,392	3,111
17	409	361	245
18	4,691	3,881	3,923
19	1,090	652	1,081
20	1,944	1,269	1,702
Mean	8,646	5,735	3,536
Standard deviation	±8,063	±6,824	±4,117
Standard error	1,803	1,526	920
Plasma metoprolol level	0	33 ng/ml (8.6–210)	72 ng/ml (17–178)
Standard deviation	0	22 ng/ml	34 ng/ml

* $p < 0.001$ versus placebo, $p < 0.02$ versus low-dose metoprolol.

Results

Efficacy of metoprolol in suppressing ventricular arrhythmias: During 3 days of placebo ambulatory electrocardiographic recording, the mean premature ventricular beat frequency was 8,640/24 hours (Table I). Three days of low-dose metoprolol (25 mg orally 4 times daily) resulted in a mean reduction of PVB to 5,735/24 hours ($p < 0.01$ versus placebo). After 4 days of ambulatory electrocardiographic recording with high-dose metoprolol (50 mg orally 4 times daily), the mean frequency of PVB was further reduced to 3,536/24 hours ($p < 0.001$ versus placebo, $p < 0.02$ versus low-dose metoprolol). Of the 20 patients, 13 had ≥50% reduction in total PVB, 8 had >70% reduction, and 4 patients had >90% reduction in PVB.

Quantitation of ventricular couplets (Table II) revealed a progressive decrease in mean couplet frequency with low- and high-dose metoprolol—a maximal 84% reduction—which was highly significant ($p < 0.002$). Analysis of the 10 patients with VT during placebo

TABLE II Ventricular Couplets: Placebo Versus Low- and High-Dose Metoprolol

Patient	3-Day Placebo: Mean Couplets/24 hours	3-Day Metoprolol (100 mg/day): Mean Couplets/24 hours	4-Day Metoprolol (200 mg/day): Mean Couplets/24 hours
1	104	1	3
2	8	6	1
3	46	1	1
4	18	18	6
5	39	152	1
6	713	49	50
7	1,700	965	333
8	7	1	0
9	2	0	0
10	71	7	2
11	228	2	4
12	11	9	18
13	39	9	23
14	6	3	0
15	3	1	4
Mean	200	81	30
Standard deviation	453	248	85
Standard error	117	64	22
p value versus placebo	0	<0.01*	<0.002*

* Wilcoxon signed ranks test.

ambulatory electrocardiographic recording (Table III) showed a 94% reduction during high-dose metoprolol therapy, with total abolition of VT in 6 of 10 patients ($p < 0.01$).

Ventricular arrhythmias during maximal Bruce exercise testing were analyzed in 13 patients with both placebo and metoprolol dosing. During the placebo test, 10 of 13 patients had PVB during exercise or in the recovery phase, 7 of 13 had couplets, and 3 of 13 had exercise-induced VT. With metoprolol, in addition to an overall 70% decrease in total PVB, there was total abolition of couplets in 5 of 7 patients and elimination of exercise-induced VT in all patients.

TABLE III Ventricular Tachycardia (VT): Placebo Versus Low- and High-Dose Metoprolol

Patient	3-Day Placebo: Mean VT Runs/24 hours	3-Day Metoprolol (100 mg/day): Mean VT Runs/24 hours	4-Day Metoprolol (200 mg/day): Mean VT Runs/24 hours
1	7	1	1
2	2	0	0
3	2	0	0
4	25	1	1
5	7	3	1
6	127	29	5
7	2	0	0
8	31	0	0
9	5	0	0
10	3	1	1
Mean	22.7	3.8	0.75
Standard deviation	40.6	9.5	1.8
Standard error	13.5	3.2	0.6
p value versus placebo	0	<0.01*	<0.01*

* Wilcoxon signed ranks test.

In addition to the demonstrated reduction in mean heart rate with metoprolol, the degree of beta blockade was further verified by a decrease in double product during maximal Bruce exercise testing from placebo (23,237 ± 5,368) to high-dose metoprolol (15,500 ± 3,548) despite comparable exercise duration (6.32 ± 1.81 minutes versus 6.88 ± 2.07 minutes, placebo versus metoprolol therapy, respectively; difference not significant).

Metoprolol plasma levels: During low doses of metoprolol (100 mg/day) peak mean plasma metoprolol levels 2 hours after a dose were 33 ± 22 ng/ml. Peak mean plasma metoprolol levels at 200 mg/day dosage were 72 ± 34 ng/ml. Trough mean plasma metoprolol levels (5 hours after dosing) during high-dose metoprolol were 41 ± 45 ng/ml.

Mean heart rate for each 24 hours was quantitated over the 10-day period with continuous ambulatory electrocardiographic recording. There was a highly significant ($p < 0.001$) incremental decrease in the mean heart rate from placebo (78 ± 8 beats/min) to low-dose metoprolol (72 ± 6 beats/min, mean peak plasma metoprolol level 33 ± 22 ng/ml) and high-dose metoprolol (62 ± 4 beats/min, mean plasma metoprolol level 72 ± 34 ng/ml).

The peak plasma metoprolol level achieved during steady-state dosing in each patient during high-dose therapy is seen in Figure 1. There was no relation to this plasma level and the percent reduction of PVB on that day of ambulatory electrocardiographic recording ($p < 0.12$).

The relation between the mean heart rate during the hour each plasma metoprolol level was obtained (both peak and trough levels) is seen in Figure 2. There was a statistically significant correlation between plasma metoprolol concentration and the mean heart rate for the specific hours sampled ($r = 0.41$, $p < 0.001$).

Relationship of metoprolol therapy to ventricular function: Two-dimensional echocardiograms performed during placebo dosing demonstrated a mean resting left ventricular ejection fraction of 50 ± 10%

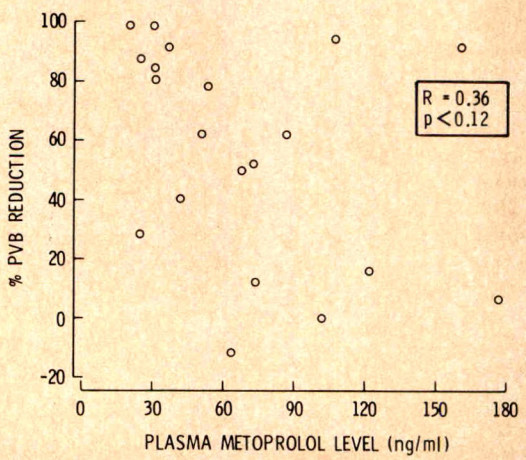

FIGURE 1. Relation of premature ventricular beat (PVB) reduction to maximal plasma metoprolol level achieved.

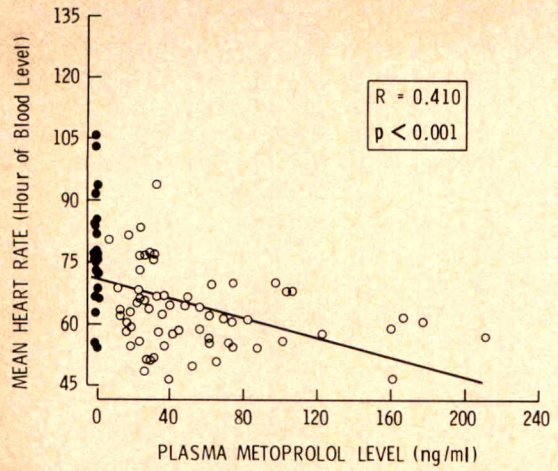

FIGURE 2. Mean heart rate during normal activity relative to metoprolol plasma concentration. **Closed circles,** placebo; **open circles,** metoprolol.

(range 22 to 71). There was no statistical difference in the ejection fraction with 200 mg/day of metoprolol (mean 48 ± 9.2%, range 31 to 68). No patient required discontinuation from the study because of clinical congestive heart failure; however, 1 patient did require increasing diuretic therapy while taking metoprolol (placebo ejection fraction of 32%, unchanged with metoprolol). Of the 4 patients with resting left ventricular ejections <40% with placebo, none had a further decrease in ejection fraction while taking metoprolol.

Relationship of metoprolol therapy to pulmonary function: Baseline pulmonary functions obtained in 18 patients during the placebo period revealed normal ventilatory function in 6, a mild restrictive defect in 4 (total lung capacity 80 to 90% predicted with normal FEV_1/FVC ratios), and obstructive airways disease in 8 (5 with FEF [25-75] <60% and normal FEV_1/FVC ratios, and 3 with FEF [25-75] <60% and reduced FEV_1/FVC ratios).

The mean FEV_1 during placebo therapy expressed as a percentage of predicted value was 89 ± 21%. After the first dose of 25 mg of metoprolol, the mean FEV_1 decreased to 85 ± 20% of predicted ($p < 0.013$). After 3 days of low-dose therapy, there was a further decrease in mean FEV_1 to 80 ± 23% of predicted ($p < 0.005$). After the first dose of 50 mg of metoprolol, this decrease was sustained; the mean FEV_1 was 81.5 ± 21% ($p < 0.001$) (Fig. 3).

The FVC and FEF (25 to 75) followed similar patterns. During placebo therapy, the mean FVC was 86 ± 11% of predicted, which decreased to 82 ± 14% with low-dose metoprolol, and to 80 ± 15% of predicted during the high-dose regimen ($p < 0.05$). The FEF (25 to 75) was 67 ± 38.5% before and 55 ± 29% after the first dose of metoprolol ($p < 0.037$), with no decrease during further dosing.

The changes in functional residual capacity, FEV_1, and FEF (25-75) induced by metoprolol were obliterated by the administration of aerosolized metaproterenol (Fig. 4). There were no differences in the groups when peak expiratory flow rates, airway resistance, specific conductance, thoracic gas volume, and total lung capacity were analyzed and compared. Arterial blood gases were unaffected by metoprolol therapy.

Despite the documented deterioration of FVC, FEV_1, and FEF (25-75), only 1 patient had clinically apparent deterioration of chronic airway obstruction (baseline FEV_1 33% of predicted) which required a decrease in metoprolol dosing to 100 mg/day and supplemental bronchodilator therapy.

Discussion

This study provides previously unavailable continuous ambulatory electrocardiographic monitoring data which document the efficacy of metoprolol in suppressing ventricular arrhythmias, and thus allow comparison to data available on other beta-blockers. Coltart et al[14,15] documented "significant" suppression of PVB at a plasma propranolol level of 40 to 85 ng/ml, a level which was also associated with significant beta blockade. Winkle et al[5] demonstrated at least a 75% reduction in PVB in 5 of 9 patients with mitral valve prolapse who were taking propranolol doses of 160 mg/day. Woosley et al[16] demonstrated a 70% suppression of PVB at a

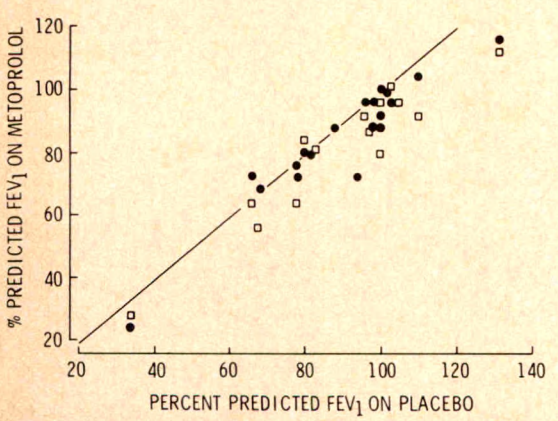

FIGURE 3. Percent change in FEV_1, placebo versus metoprolol before metaproterenol. FEV_1 = forced expiratory volume in 1 second. **Closed circles,** metoprolol, 100 mg/day; **open squares,** metoprolol, 200 mg/day.

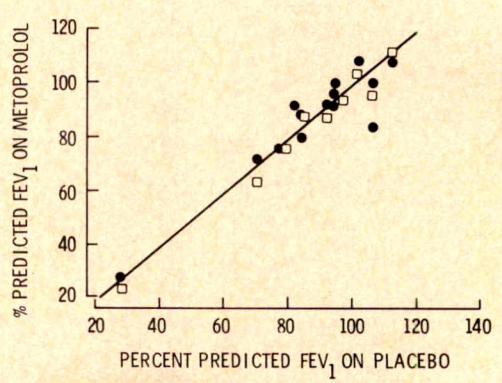

FIGURE 4. Percent change in forced expiratory volume in 1 second (FEV_1): placebo versus metoprolol after metaproterenol. **Closed circles,** metoprolol, 100 mg/day; **open squares,** metoprolol, 200 mg/day.

wide range of plasma propranolol levels (12 to 1,100 ng/ml). Interestingly, only one third of the patients responded at <160 mg/day of propranolol, while an additional 40% responded at propranolol doses of 200 to 640 mg/day. Thus, propranolol doses and plasma propranolol levels were frequently higher than comparable metoprolol doses in the present protocol. Propranolol has also been documented to suppress VT, especially if induced by exercise, a finding similar to the results of the present study.[3,17,18] Documentation of the ventricular antiarrhythmic effect of other beta-blockers, including tolamolol, alprenolol, and pindolol, lack studies utilizing long-term continuous ambulatory electrocardiographic recordings.[19–21] The duration of ambulatory electrocardiographic recording is crucial for appropriate evaluation of drug efficacy since recent studies emphasize a significant daily variability of ventricular arrhythmias.[22,23] In the present study, metoprolol at a dose of 100 mg/day suppressed only 34% of PVB, whereas 200 mg/day resulted in an overall 60% suppression of PVB. According to the data of Morganroth et al,[22] a 65% suppression of PVB is required to rule out variability as the cause of change in premature ventricular beat frequency in individual patients utilizing 3 days of placebo ambulatory electrocardiographic data and 3 days with the drug. By this criteria, high-dose metoprolol was "effective" in 50% of the 20 patients studied. The improved suppression of couplets (84%) and VT (94%), as well as abolition of exercise-induced VT, are all consistent with published observations of propranolol.[3,17]

This study also provides new information on plasma metoprolol levels achievable on routinely used dosage regimens as well as the degree of beta blockade demonstrated. High-dose metoprolol lowered the mean 24-hour heart rate from 78 to 62 beats/min while achieving a mean peak plasma metoprolol level of 72 ng/ml. This 20% decrease in the mean hourly heart rate during normal activity is similar to the 20 to 30% reduction in peak heart rate-blood pressure product documented by maximal exercise testing in this study. The wide range of peak plasma metoprolol levels (17 to 178 ng) obtained at steady-state doses of 200 mg daily are consistent with highly variable plasma propranolol levels[15,16] and emphasize the importance of clinical parameters to assess beta blockade. The lack of deterioration of resting left ventricular function or evidence for precipitation of clinical congestive heart failure even in patients with moderately depressed left ventricular function documents similar observations with other beta-blockers, even in the setting of acute myocardial infarction.[24–27,29] Experience from the National Beta-Blocker Heart Attack Trial demonstrated the ability of patients to tolerate significant doses of propranolol (160 to 320 mg/day) despite compensated congestive heart failure requiring digitalis and diuretics.[7] Similar observations were made during the Norweigan Metoprolol Trial, even with the use of intravenous metoprolol in the setting of acute myocardial infarction.[9]

Pulmonary function data were obtained because the use of metoprolol in many patients with obstructive lung disease may be desirable since the administration o nonselective beta-adrenergic blocking agents is pre cluded by bronchospasm. Several investigators hav documented the relatively cardioselective effects o metoprolol compared with propranolol in patients wit chronic bronchitis and asthma, although many reporte studies used single metoprolol doses. Tivenius,[28] how ever, found little effect of metoprolol on ventilator function in chronic airway obstruction after 4 doses o metoprolol; Formgren[29] documented a dose-relate effect on FEV_1 in asthmatic patients taking metoprolo who were studied over a 17-day interval.

The current study illustrates the spectrum of func tional ventilatory abnormalities that can be expecte in patients with cardiac disease receiving metoprolol i doses to achieve a peak mean plasma metoprolol leve of 72 ng/ml. We document the negative effects on FEV_1 FEF (25-75), and FVC, but emphasize that clinicall significant deterioration in ventilatory function occur only in a few select patients. The changes in FVC an FEV_1 are somewhat greater in our study than in report by McGavin and Williams[30] and Sinclair.[31] This ma be explained by our timing of pulmonary function test 2 hours after the test dose when drug levels are nea peak. These changes in FEV_1 and FVC could not b explained due to alterations in left ventricular functio with concomitant increase in lung water since there wa no evidence of further echocardiographic or clinical lef ventricular dysfunction with metoprolol.

Of the several patients who had measurable ob structive defects with decreasing FEV_1/FVC ratios an increasing airway resistance with metoprolol, only 1 ha clinically significant wheezing. With the exception o that patient's response, the group data suggest tha bronchodilator therapy obliterated these changes i FVC and FEV_1 induced by metoprolol. This furthe substantiates the findings of Thiringer and Svedmyr[3] and Johnson,[33] who reported that ventilatory change induced by metoprolol were readily reversed by beta adrenergic agonists but that those induced by pro pranolol were not. The availability of selective beta-adrenergic agonists such as albuterol may make con comitant therapy desirable, allowing the use of me toprolol when clinically indicated in these patients.

Our data further suggest that spirometry performe before and 2 hours after the first dose of metoprolol i useful to screen for pulmonary intolerance to beta blocking agents. A decrease in FVC or FEV_1 of >20 from baseline would mandate special caution and con stitute a relative contraindication to use of beta blockers. A decrease of 10 to 20% from baseline coul be corrected by the addition of a beta-2 selective agonis if the use of beta-blockers was indicated.

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Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Tablets of 50 mg
Tablets of 100 mg

Prescribing Information

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors of malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications**, **Warnings**, and **Precautions**.

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings**.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
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The original cardioselective beta blocker is now... Lopressor® metoprolol tartrate Today

Experts state preference for beta-one receptors; this preference is not absolute.

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Avoid any change in the classic digitalis-Lasix® regimen.

BRAND OF (furosemide)

9 out of 10 cardiologists specify LASIX® (furosemide) by brand name.* And 2 out of 3 take the extra step to prevent substitution.*

7 out of 10 cardiologists also specify the leading brand of digoxin.* Both are part of the classic LASIX®-digitalis regimen.

In the same survey,* LASIX® and the leading brand of digoxin were named more often than any other agent, in any therapeutic class, as drugs for which these cardiologists would *never* allow generic substitution. Both were prescribed by brand name more often than any other drug.

LASIX®—specified for good reason.

Especially in CHF, precision is crucial. Any therapeutic variable could easily upset the sensitive digitalis/diuretic/electrolyte balance and precipitate digitalis toxicity.

LASIX®, the most thoroughly documented drug in its class, offers quality so consistent that almost 8 billion tablets have been manufactured without a single product recall. In more dosage strengths and forms than any other diuretic. Good reason for the cardiologists surveyed to say they prescribe LASIX® more frequently than all other diuretic agents they named.

Before prescribing, please consult complete product information, a summary of which appears on the following page.

*National survey of 2960 physicians, including 1502 cardiologists and other physicians subspecializing in cardiology, conducted by Hoechst-Roussel Pharmaceuticals Incorporated, Somerville, New Jersey. August, 1982.

The diuretic of choice in CHF.

LASIX®

20 mg
40 mg
80 mg
Tablets

BRAND OF (FUROSEMIDE)

Rx

Specify LASIX® brand of furosemide. To be sure the patient receives only LASIX®, take the steps necessary on your prescription to prevent substitution, in accordance with the regulations of your state.

Lasix 40mg #60
Sig. 1 b.i.d.
Do Not Substitute

LASIX® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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From the American Journal of Medicine

NOSOCOMIAL INFECTIONS

edited by
Richard E. Dixon, M.D.

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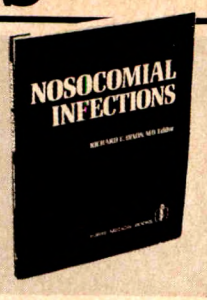

Based on the proceedings of the 2nd International Conference on Nosocomial Infections held August 5 - 8, 1980 in Atlanta, Georgia and sponsored by the Center for Disease Control, this book provides between two covers the most comprehensive, in-depth study of this international problem published in 10 years. This major reference is divided into 11 sections consisting of 50 chapters written by over 100 internationally known experts.

The book includes:

- An update of disease trends since the 1st International Conference held a decade earlier
- New information on the efficacy of specific approaches to infection control
- Discussions on how to implement effective infection surveillance and control programs
- Coverage of the increasing importance of antimicrobial resistance of nosocomial pathogens
- Information on the potential usefulness of antimicrobial prophylaxis in selected patient groups

and many other topics.

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FACT: Not any more. Advanced semiconductor technology makes the MIKRO-TIP® Catheter Pressure Transducer durable . . . so durable it can be used *routinely* again and again and again.[1]

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mean half-life
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flurazepam)

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Too long a half-life may lead to:
- drug accumulation
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Some benzodiazepine hypnotics have <u>too short</u> a half-life

Too short a half-life may lead to:
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- anterograde amnesia

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Restful sleep, alert awakening

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15 mg
30 mg
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(temazepam)
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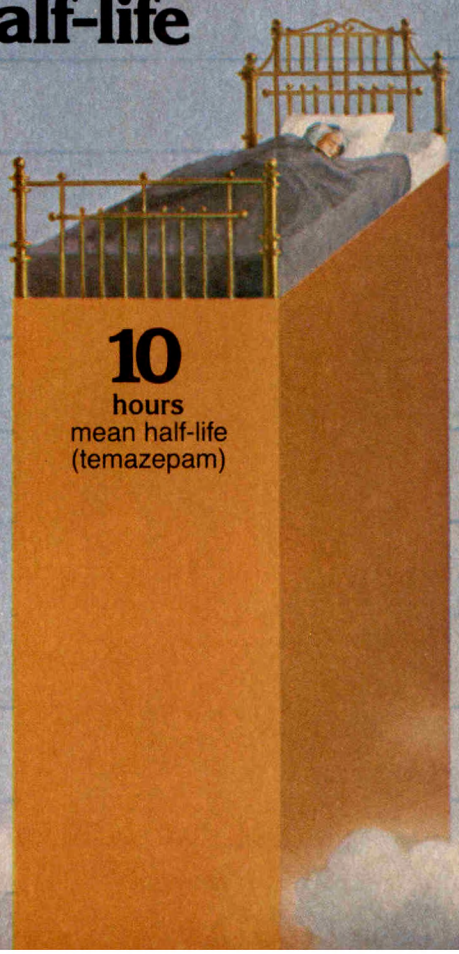

A half-life (mean of 10 hours) that parallels normal sleep time:

- patient gets 7-8 hours sleep
- most medication gone by morning
- patient awakes alert and refreshed
- minimal side effects•
- insignificant accumulation

Please see brief summary of prescribing information on next page.

Restful sleep, alert awakening

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(temazepam)

A more appropriate half-life

One 30-mg capsule, h.s.—*usual adult dosage.*
One 15-mg capsule, h.s.—*recommended initial dosage for elderly and/or debilitated patients.*

INDICATIONS AND USAGE: Restoril® (temazepam) is indicated for the relief of insomnia associated with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment should be considered.

CONTRAINDICATIONS: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in neonatal CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

WARNINGS: Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

PRECAUTIONS: In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

Information for Patients: Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tests: The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Pregnancy: Pregnancy Category X. See Contraindications.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The most common adverse reactions were drowsiness, dizziness and lethargy. Other side effects include confusion, euphoria and relaxed feeling. Less commonly reported were weakness, anorexia and diarrhea. Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations. And rarely reported were hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity.

Restoril is a controlled substance in Schedule IV. Caution must be exercised in addiction-prone individuals or those who might increase dosage.

DOSAGE AND ADMINISTRATION: *Adults:* 30 mg usual dosage before retiring; 15 mg may suffice in some. *Elderly and/or debilitated:* 15 mg recommended initially until individual response is determined.

SUPPLIED: Restoril (temazepam) capsules—15 mg maroon and pink, imprinted "RESTORIL 15 mg"; 30 mg, maroon and blue, imprinted "RESTORIL 30 mg". Packages of 100, 500 and ControlPak® packages of 25 capsules (continuous reverse-numbered roll of sealed blisters). (RES-Z2 11/1/81)

Before prescribing, see package insert for full product information.

RES-183-2

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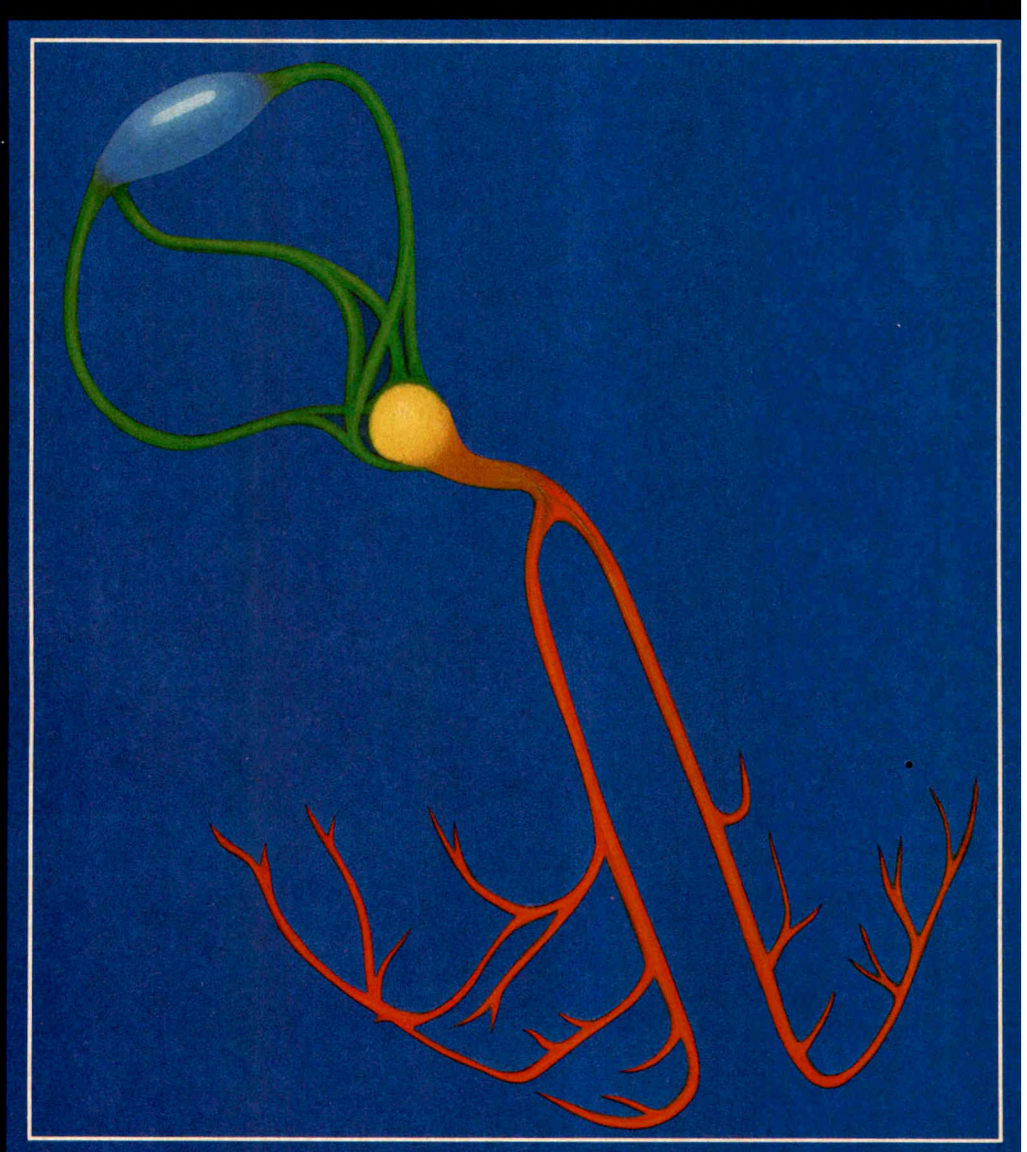

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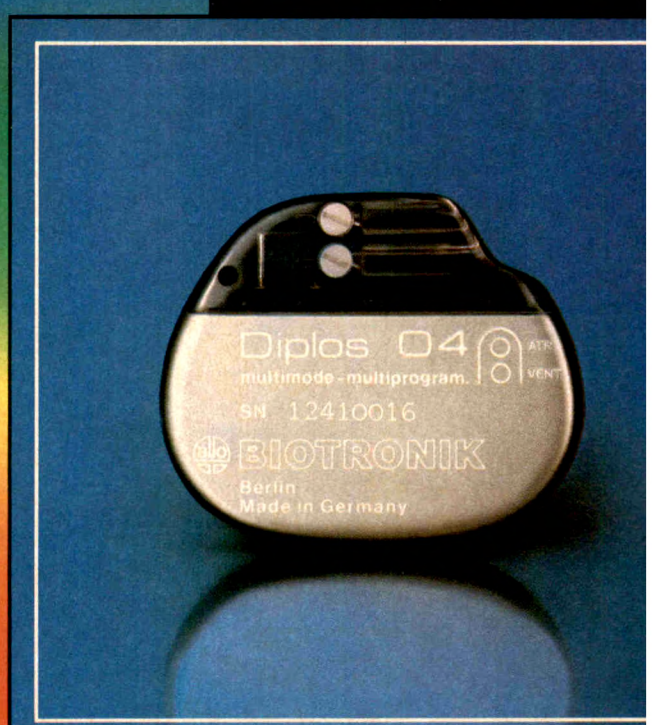

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PRINT: provides a pacemaker program print-out

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* The EPR 500 can be used to program all programmable BIOTRONIK pacemakers.

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Pacemaker system currently undergoing clinical evaluation.

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Side effects. The following is a list of side effects which

of pulse generator: transvenous lead-related thrombosis and cardiac tamponade.

Warnings. Diathermy should not be used on patients with implanted pacemakers. The use of electrosurgical instruments in the presence of unipolar pulse generators must be avoided. If the paddles of a defibrillator are placed over

Precautions. An implanted pacemaker may fail at any time due to unpredictable battery or other random component failures. Furthermore problems caused by leads, e.g. displacement, fracture, fibrotic tissue, raised threshold, can stop pacing at any time. Electrical interference may effect the correct operation of an implanted pacemaker.

Syncope and Ventricular Tachycardia in Patients With Ventricular Preexcitation

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Four patients with ventricular preexcitation whose syncope initially was attributed to an arrhythmia utilizing the accessory pathway are presented. At electrophysiologic study, the electrophysiologic characteristics of the accessory pathways were considered unlikely to support a tachycardia of a rate sufficient to result in syncope. Programmed stimulation of the right ventricle, however, reproducibly induced ventricular tachycardia to which the syncope was subsequently attributed in 3 patients. The importance of identifying ventricular tachycardia as the cause of syncope in these patients is emphasized.

Patients who have ventricular preexcitation may present with syncope which often is assumed to be related to an arrhythmia utilizing the accessory pathway. Atrial fibrillation (AF) with a rapid ventricular response due to conduction over an accessory pathway is probably the most common cause of syncope in these patients, although a rapid atrioventricular reciprocating tachycardia also may cause a decrease in cardiac output and loss of consciousness. In older patients with cerebrovascular disease in whom minor reductions in cardiac output can reduce cerebral perfusion significantly and in patients with impaired myocardial function, relatively slower supraventricular tachycardia rates may result in syncope or presyncope. Ventricular tachycardia (VT) often causes syncope, but the occurrence of VT in patients with ventricular preexcitation rarely has been documented by electrophysiologic study.[1,2] We present 4 patients with accessory pathways who at electrophysiologic study had VT induced, which was considered to be the cause of neurologic symptoms in 3 patients.

Methods

After admission to a cardiac care unit where their cardiac rhythms were monitored continuously, all patients underwent electrophysiologic study in the drug-free control state after giving written informed consent. Three or 4 multipolar electrode catheters were introduced percutaneously into the femoral, subclavian, or antecubital veins and positioned under fluoroscopic guidance in the high right atrium, across the tricuspid valve in the region of the His bundle, in the right ventricular apex, and in the coronary sinus. Intracardiac recordings filtered at 30 to 500 Hz and standard electrocardiographic leads I, II, III, and V_1 filtered at 0.1 to 20 Hz were displayed simultaneously on an Electronics for Medicine VR-12 multi-channel oscilloscope and recorded at paper speeds of 50 to 150 mm/s. Pacing was performed with a custom built programmable stimulator (MECA) using 2.0 ms rectangular pulses at twice late diastolic threshold.

Our pacing protocol to study the electrophysiologic properties of accessory pathways and to initiate supraventricular and ventricular tachycardias has been described in detail.[3,4] In brief, the right or left atrium (or both) was paced at progressively faster rates until atrioventricular block occurred; premature right atrial and coronary sinus stimulation was performed at ≥2 cycle lengths. Programmed right ventricular stimulation during sinus rhythm and right ventricular pacing at 3 cycle lengths (600, 500, and 400 ms) was carried out using 1 and 2 extrastimuli at various coupling intervals.

VT was defined as nonsustained when it lasted <30 seconds and did not cause hemodynamic deterioration requiring termination.

Patients: All 4 patients were men in whom the resting electrocardiogram revealed ventricular preexcitation (Table I). They were referred for further evaluation of syncope (3 cases) or presyncope (1 case) attributed to an arrhythmia utilizing the accessory pathway. In 2 patients (Patients 1 and 4), a wide QRS complex tachycardia had been recorded at the time of syncope but was unavailable for our inspection.

Patients 1 and 3 had no evidence of structural heart disease observed on physical examination, chest roentgenography, exercise stress test, and echocardiography, and patient 1 had normal coronary arteries and left ventricular function defined by cardiac catheterization. Patient 2 had a history of hypertension and a thickened left ventricle documented by echocardiography. He had no history of chest pain and a normal exercise stress test. Patient 4 had a previous myocardial infarction and total obstruction of the left anterior descending coronary artery associated with an anteroapical aneurysm noted at cardiac catheterization.

From the Krannert Institute of Cardiology, the Department of Medicine, Indiana University School of Medicine, and from the Veterans Administration Medical Center, Indianapolis, Indiana. This study was supported in part by the Herman C. Krannert Fund Indianapolis, Indiana; by Grants HL-06308 and HL-07182 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; by the American Heart Association, Indiana Affiliate, Indianapolis, Indiana; and by the Veterans Administration, Indianapolis, Indiana. Manuscript received October 27, 1982; revised manuscript received and accepted March 25, 1983.

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TABLE I Patient Characteristics

Patient	Age (yr)	Heart Disease	Symptoms			Treatment	Follow-Up Symptoms
			Presenting	Frequency	Duration		
1	22	None	Syncope	2 episodes	2 weeks	Encainide	5 months, none
2	47	Hypertensive	Syncope	Twice weekly	10 years	Procainamide	12 months, palpitations, presyncope
3	30	None	Presyncope	Daily	1 month	Quinidine	13 months, none
4	50	CAD	Syncope	5 episodes	4 years	None	18 months, none, CHF

CAD = coronary artery disease; CHF = congestive heart failure.

TABLE II Electrophysiologic Characteristics

Patient	Location of Pathway	Shortest PCL With 1:1 Anterograde Conduction Over AP (ms)	Anterograde ERP of AP at PCL (600 ms)	Shortest R-R During A Fib (ms)	Mean R-R During A Fib (ms)	Shortest PCL Maintaining 1:1 Conduction Retrograde (ms)	Mode of VT Induction*	Mean Cycle Length of VT (ms)
1	Left-lateral	330	290	310	500	VA block	V_2V_3 (500, 400 ms)	170
2	Right-† lateral	310	290	Not inducible	Not inducible	VA block	V_2V_3 (400 ms)	220
3	Right-anterior-paraseptal	<250	300	270	380	270	A_2;V_2V_3 (600,500 ms)	240
4	Left-posterior	>870	>600	Not inducible	Not inducible	540	V_2V_3 (500, 400 ms)	275

* Pacing cycle length is given in parentheses.
† This patient also had an accessory fasciculoventricular connection.
A_2 = 1 atrial extrastimulus introduced during normal sinus rhythm; A Fib = atrial fibrillation; AP = accessory pathway; ERP = effective refractory period; PCL = pacing cycle length; V_2V_3 = 2 ventricular extrastimuli introduced during ventricular pacing; VA = ventriculoatrial; VT = ventricular tachycardia.

Results

Atrioventricular reciprocating tachycardia could not be induced in any of the patients despite programmed electrical stimulation at multiple pacing cycle lengths in the right atrium, coronary sinus, and right ventricle. The electrophysiologic data of all 4 patients are shown in Table II. Nonsustained VT was induced in all patients using 2 premature stimuli while pacing the right ventricle. Patient 1 had presyncope during the induced VT (Fig. 1). In patient 3, nonsustained VT also was induced by an atrial extrastimulus during sinus rhythm (Fig. 2).

Patients 1 and 2 had complete ventriculoatrial block in the accessory pathway and in the normal ventriculoatrial conduction system (Fig. 3). In Patient 3 ventricular pacing resulted in a normal retrograde atrial activation sequence and ventriculoatrial conduction was maintained to a cycle length of 270 ms with no increase in the ventriculoatrial interval at the shortest pacing cycle length. These combined findings suggest retrograde conduction over a septal accessory pathway, but do not exclude retrograde conduction over the normal ventriculoatrial conduction system.[5] In Patient 4 ventriculoatrial block occurred while pacing the ventricle at a cycle length of 540 ms.

In Patient 2, the presence of an accessory fasciculoventricular pathway in addition to an accessory atrioventricular pathway was demonstrated (Fig. 4). The short H-V interval remained constant throughout multiple catheter positions at the His bundle area.

Follow-up (Table I): Patient 1 underwent serial electrophysiologic testing; encainide therapy prevented initiation of VT and he has had no recurrence of symptoms. Patient 2 was given procainamide that abolished anterograde conduction over the accessory pathway but did not prevent VT induction at electro-

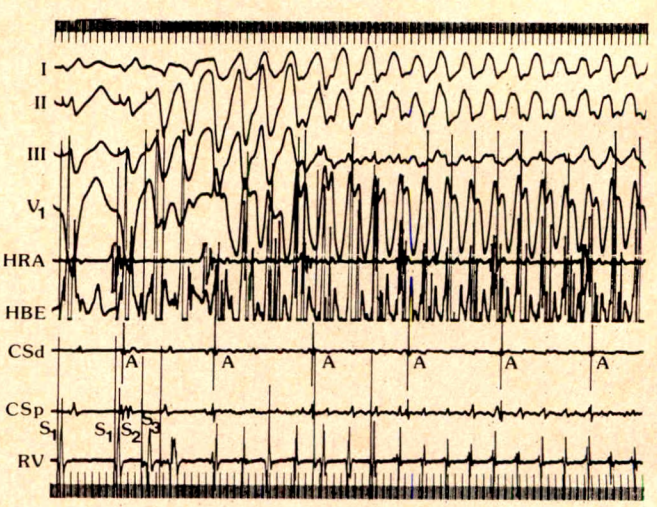

FIGURE 1. Induction of ventricular tachycardia at a rate of 353 beats/min (Patient 1). The top 4 tracings are electrocardiographic leads I, II, III, and V_1. The bottom 5 tracings are electrograms recorded from catheters in the high right atrium (HRA), His bundle area (HBE), distal coronary sinus (CSd), proximal coronary sinus (CSp), and right ventricular apex (RV). The right ventricle is being paced (S_1-S_1 400 ms); 2 premature stimuli (S_2-S_3) are introduced resulting in rapid monomorphic ventricular tachycardia at a mean cycle length of 170 ms. The CSd electrogram demonstrates ventriculoatrial dissociation. Time lines = 50 ms/major division.

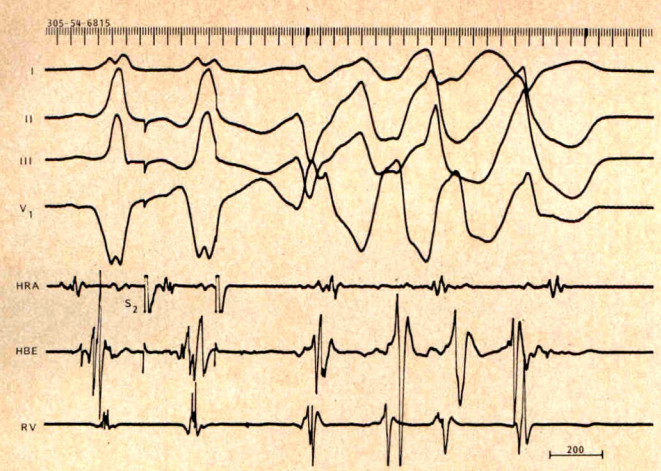

FIGURE 2. Induction of ventricular tachycardia during atrial premature stimulation. An atrial extrastimulus (S_2) with a coupling interval of 330 ms conducts to the ventricle over the accessory pathway and initiates nonsustained ventricular tachycardia. A second stimulus artifact 270 ms after S_2 fails to capture the atrium. Abbreviations as in Figure 1.

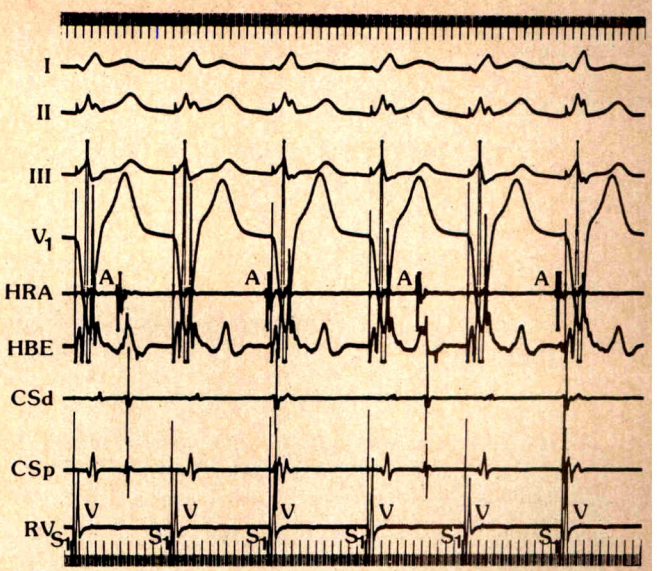

FIGURE 3. Complete retrograde block (Patient 1). The right ventricle is being paced (S_1) at a cycle length of 600 ms, there is ventriculoatrial dissociation, the atrial complexes (A) occurring regularly at a cycle length of 900 ms. Abbreviations as in Figure 1.

physiologic study. He refused further testing, was discharged taking procainamide, and has monthly episodes of presyncope and palpitations. Patient 3 was treated empirically with quinidine. Ventricular preexcitation was unaffected but the patient was asymptomatic for 13 months of follow-up study. Of note, palpitations occurred when the patient voluntarily stopped taking quinidine. Patient 4 did not want to take antiarrhythmic drugs and has had no recurrence of syncope but developed congestive heart failure. It should be noted that at least 2 of his syncopal episodes were associated with heavy alcohol consumption, and it is not clear that VT was responsible for his episodes of syncope.

Discussion

The electrophysiologic properties of 322 patients with ventricular preexcitation combined from 2 reports reveal that only 2 had VT independent of their accessory pathways,[1,2] confirming that this is a rare occurrence. It clearly is important to identify those patients whose syncope is caused by ventricular tachycardia and not by reciprocating tachycardia using the accessory pathway as part of the reentrant circuit or AF with a rapid ventricular response over the accessory pathway, for the treatment of these various arrhythmias may differ.

In patients with ventricular preexcitation and an accessory pathway with a short anterograde effective refractory period, the occurrence of AF may result in very rapid ventricular rates due to conduction over the accessory pathway. This may produce syncope and

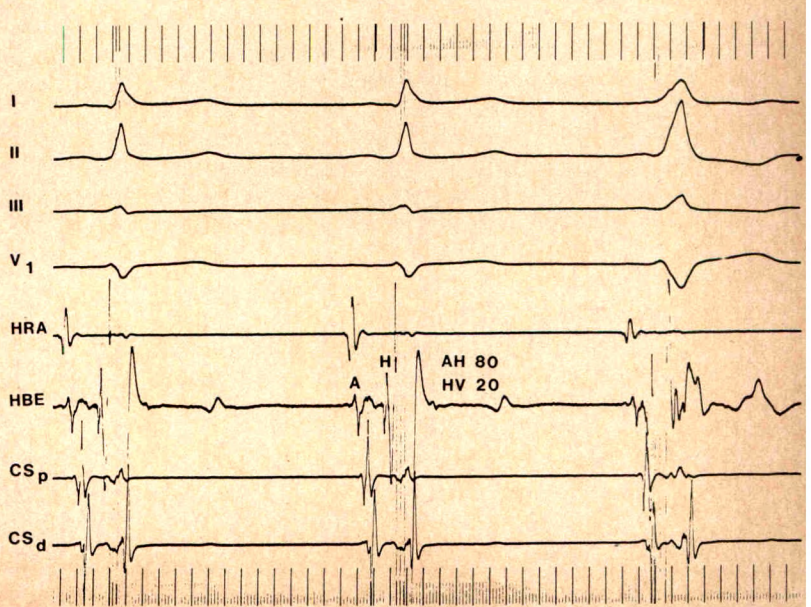

FIGURE 4. Atrioventricular and fasciculoventricular accessory pathways (Patient 2). The first 2 complexes demonstrate an H-V interval of 20 ms which persisted throughout the study, confirming the presence of an accessory fasciculoventricular pathway. This was the longest H-V interval recorded throughout the study. In the third complex, the His deflection is buried in the QRS complex while the surface electrocardiogram demonstrates ventricular preexcitation, confirming the presence of an accessory atrioventricular connection.

possible degeneration of the rapid rhythm into ventricular fibrillation (VF). It has been observed that the shortest R-R interval during AF in 14 of 18 such patients with VF was <205 ms.[2] In Patients 1 and 3, in whom AF was induced, the shortest R-R interval was 310 and 270 ms, respectively. This observation is consistent with the conclusion that VF resulting from a rapid ventricular response to AF was not the cause of the syncope in these 2 patients. Furthermore, the mean R-R interval during AF in these 2 patients was 500 and 380 ms, respectively, cycle lengths unlikely to have resulted in syncope in these 2 young, otherwise healthy persons.

In Patients 2 and 4, AF could not be induced and therefore could not be excluded as a cause of their syncope. However, the relation between the effective refractory period of the accessory pathway in the anterograde direction and the shortest R-R interval during AF has been demonstrated to be linear.[6] Applying these data[6] to Patients 2 and 4, whose effective refractory periods of the accessory pathway in the anterograde direction were 290 and >600 ms, respectively, the shortest R-R interval in response to AF would have been on the order of 290 and 600 msec, respectively, which is considerably longer than the shortest R-R interval of those patients who had VF.[2] In a second study,[7] all but 2 of 21 patients who had VF had anterograde effective refractory periods of the accessory pathway <290 ms. It is therefore unlikely that AF would have resulted in VF in these patients.

In addition to allowing a rapid ventricular response to AF or flutter, accessory pathways may lead to syncope by participating in the circuit of an atrioventricular reciprocating tachycardia, if the rate is fast enough. However, the inability to induce reciprocating tachycardia in the laboratory in these 4 patients despite programmed stimulation at multiple sites and cycle lengths makes this mechanism of syncope highly improbable.[8] Thus, the electrophysiologic data of these patients suggest that the accessory pathway was incapable of participating in an arrhythmia that would have caused sufficient hemodynamic disturbance to result in syncope.

Although the induced VT in these 4 patients as the cause of syncope is not entirely proven, 2 of them had a wide QRS complex tachycardia documented at the time of syncope; the electrophysiologic data indicate that this is not likely to have been the result of AF conducted over the accessory pathway. Furthermore, ventricular tachycardia induced by programmed electrical stimulation using only 1 or 2 extrastimuli and not isoproterenol or left ventricular stimulation suggests that the arrhythmia occurs clinically[9–11] and the incidence of false-positive findings in patients without structural heart disease, using these stimulation techniques, is very low.[12] In Patients 1 and 3, therefore, there is good evidence that VT was the cause of their syncope. However, more recent data suggest that VT can be induced in patients with coronary artery disease but without a history of VT.[13] Thus, VT induced in Patient 4 may have been a false-positive result.

Although only nonsustained VT was induced at electrophysiologic study in Patient 2, we feel that his clinical symptoms were due to more prolonged episodes of VT. It is not always possible to induce sustained ventricular tachycardia using the aforementioned techniques (Methods) in patients who have electrocardiographically proven sustained VT as we[14] have previously published. Further, although procainamide therapy has abolished anterograde accessory pathway conduction, the patient remains symptomatic.

Addendum

We recently performed an electrophysiologic study on a 41-year old-woman with Wolff-Parkinson-White syndrome but with no other identifiable structural heart disease. She had a history of 4 syncopal attacks, 2 resulting in fractures of her arm and leg. The electrocardiogram showed ventricular preexcitation in sinus rhythm, but no conduction occurred over the accessory pathway during AF initiated during electrophysiologic study. Ventriculoatrial dissociation occurred at all ventricular pacing cycle lengths. Multiple episodes of nonsustained VT were induced during ventricular pacing at a cycle length of 600 ms using 2 extrastimuli. The tachycardia cycle length was 220 ms (272/min), and 1 episode resulted in loss of consciousness before spontaneous termination. This patient's symptoms cannot be explained by arrhythmias involving the accessory pathway, and are most likely due to VT.

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Efficacy, Safety, and Pharmacokinetics of a Concentration-Maintaining Regimen of Intravenous Pirmenol

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A 3-stage, concentration-maintaining intravenous infusion regimen of pirmenol, a new antiarrhythmic agent, was tested for efficacy and safety in 8 subjects with chronic, stable premature ventricular beats. The regimen, which consisted of (1) a priming bolus of 50 mg over 2 minutes, followed by (2) a rapid loading infusion of 2.5 mg/min for 1 hour, and (3) a maintenance infusion of 0.25 mg/min, rapidly achieved and maintained stable plasma pirmenol levels from 0.94 to 2.75 μg/ml, during infusions lasting up to 48 hours. Therapeutic efficacy was evaluated during 4-hour infusions in 5 patients utilizing a randomized, double-blind, placebo-controlled study design. Pirmenol suppressed average premature ventricular beat frequency 93 ± 6% compared with control values (p = 0.03). Pirmenol infusions were unassociated with toxicity. There were slight but significant increases in diastolic blood pressure, QRS duration, and corrected Q-T interval. No significant changes occurred in systolic blood pressure, heart rate, P-R interval, or laboratory variables. Pirmenol is a promising therapeutic agent that warrants further evaluation. The 3-stage infusion satisfactorily achieves and maintains therapeutic plasma pirmenol levels.

Pirmenol (Parke-Davis, CI-845) is a new antiarrhythmic agent which has electrophysiologic properties similar to class I antiarrhythmic drugs in canine Purkinje fibers.[1] Recently, the promising canine experience[2,3] was confirmed in the first reported human studies.[4,5] In 10 subjects, 70 to 150 mg of pirmenol was administered intravenously over 30 minutes at a constant rate. Peak plasma concentrations of 1.0 to 3.8 μg/ml were produced and caused ≥90% reduction in the frequency of chronic, stable, premature ventricular beats (PVBs) in 9 of 12 instances.[4] To be clinically useful, however, intravenous pirmenol will have to be administered by an infusion regimen that rapidly achieves and maintains stable plasma concentrations. An intravenous loading and maintenance regimen has been devised using pharmacokinetic parameters calculated from the 30-minute infusions.[6] This study describes the efficacy and safety of this regimen during infusions of 4 to 48 hours in patients with PVBs.

From the Division of Cardiology, Department of Medicine, and the Division of Clinical Pharmacology, Department of Pharmacology, Duke University Medical Center, Durham, North Carolina. This study was supported by Grants RR-30 from the General Clinical Research Centers Program, Division of Research Resources and by Grants HL24920 and HL07101 from the National Heart, Lung, and Blood Institute and Grant LM03373 from the National Institutes of Health, Bethesda, Maryland. Manuscript received October 18, 1982; revised manuscript received April 4, 1983, accepted April 6, 1983.

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Methods

Subjects: A total of 8 subjects (7 men and 1 woman; mean age 54 years, range 38 to 66) with chronic stable PVBs were studied. Subjects had a mean of 960 ± 615 PVBs/hour during the control period before infusion. No subject had sustained tachycardia, sinus nodal abnormality, or conduction system delay. No person with a history of acute myocardial infarction within the previous 6 months or with severe chronic obstructive pulmonary disease were included. All antiarrhythmic drugs were discontinued at least 4 half-lives before study. Six subjects received intravenous pirmenol or placebo on successive study days (separated by a rest day) using a randomized, double-blind, crossover study design. Four of these subjects and 2 other subjects received open-label pirmenol as a prolonged infusion of 8 to 48 hours. Five subjects had previously received pirmenol in our earlier study.[4]

Four subjects had definite or probable coronary artery disease (2 had a history of myocardial infarction). Two other subjects had a history of moderate hypertension (1 of whom also had diabetes mellitus of adult onset). Two subjects had no apparent cardiac disease. No subjects had symptoms of congestive heart failure. Cardiothoracic index was ≤0.54 for all subjects (mean 0.48). Baseline 2-dimensional and M-mode

echocardiography was normal in 7 subjects and revealed mild septal hypokinesia in 1 person.

The following tests performed in all subjects before and after pirmenol infusion: 12-lead electrocardiogram, complete blood count, reticulocyte count, prothrombin time, serum electrolytes, glucose, total protein, total bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, lactic dehydrogenase, alkaline phosphatase, creatinine, blood urea nitrogen, fluorescent antinuclear antibody, creatinine phosphokinase, and urinalysis.

Pirmenol administration: The method for simulation of the plasma pirmenol concentration after complex dosage regimen has been fully described in a previous publication.[6] It involves utilizing the pharmacokinetic parameters derived from single-dose infusions. These parameters are then used to separately calculate the plasma concentration versus time curves for the priming bolus, the loading infusion, and the maintenance infusion which are then summed to yield a simulation of the dosage regimen. To design the final regimen, somewhat arbitrary decisions about the duration of the rapid loading infusion (1 hour) and maximum level after loading (2.5 μg/ml) were made.

The final regimen was a 3-stage dosing regimen consisting of (1) a priming bolus of 50 mg delivered over 2 minutes, followed by (2) a rapid loading infusion of 2.5 mg/min for 1 hour, and finally (3) a maintenance infusion of 0.25 mg/min. The rapid loading and maintenance infusions were obtained from a concentration of 2.5 mg of pirmenol per milliliter of sterile isotonic saline solution delivered at rates of 60 and 6 ml/hour, respectively, by a gravity fed controller (IVAC 230) through a 20 gauge Teflon® cannula inserted into a superficial arm vein.

Blood samples for pirmenol assay were obtained from another 20 gauge cannula in the opposite arm.

Electrocardiographic monitoring: All subjects were studied in normal sinus rhythm while resting and supine. Continuous electrocardiographic monitoring of a modified lead II (left shoulder negative, cardiac apex positive) was performed for 1 hour before, during, and for 4 hours after drug infusion using a Hewlett-Packard model 78100A and 78101A telemetry transmitter and receiver and an Elema Mingograf ink jet recorder. In addition, the coronary care unit staff monitored each subject's electrocardiogram continuously during drug infusion. A staff cardiologist determined the frequency of PVBs per half-hour period by manual analysis during both the double-blind protocol and prolonged infusions. Electrocardiographic intervals (P-R interval, QRS duration, and Q-T interval) were recorded at a paper speed of 100 mm/s at 30 minute intervals for the first 4 hours of drug infusion and then at 2 hourly intervals during prolonged pirmenol infusions. Blood pressure was determined by the cuff method.

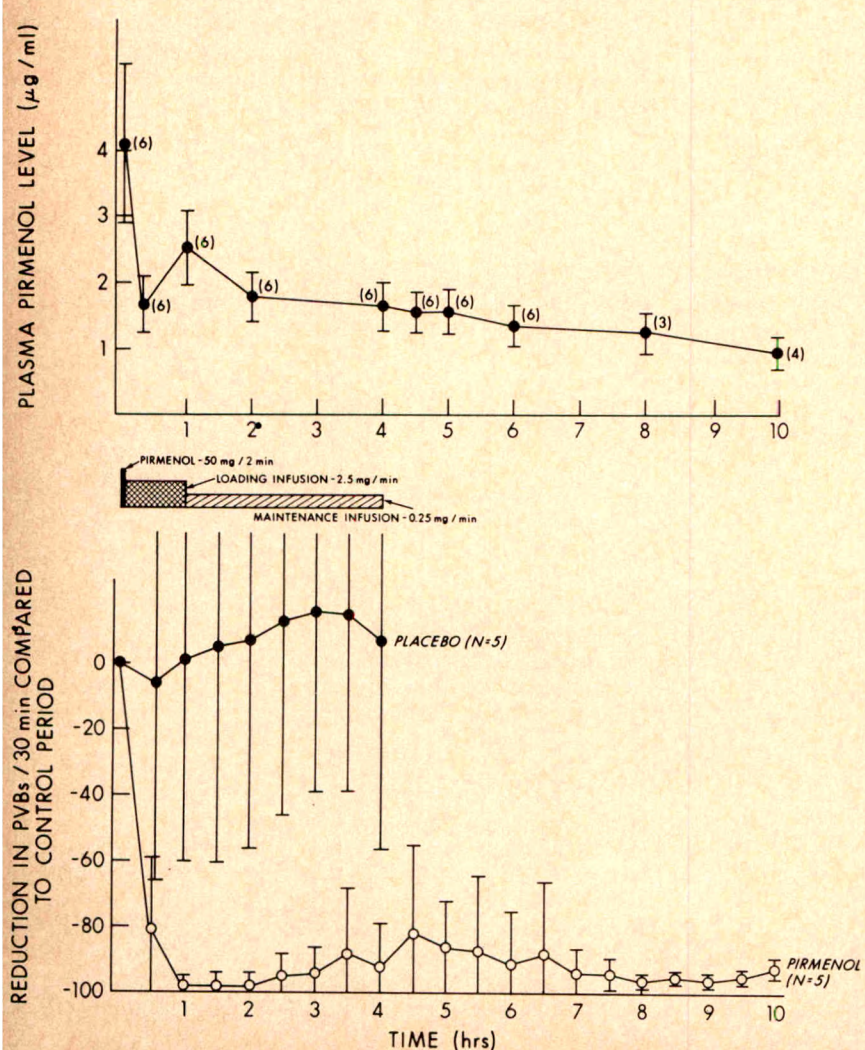

FIGURE 1. Mean plasma pirmenol concentration (**top**) and reduction in premature ventricular beat (PVB) frequency (**bottom**) during and after 4-hour infusions of pirmenol are shown. PVB frequency during placebo infusion is also shown. Pirmenol levels (mean ± standard deviation) represent data from 6 subjects participating in the double-blind placebo-controlled trial. One subject was excluded from analysis of PVB frequency when he failed to meet the inclusion criteria of at least 1 PVB/min during the lead-in control periods of both infusion days.

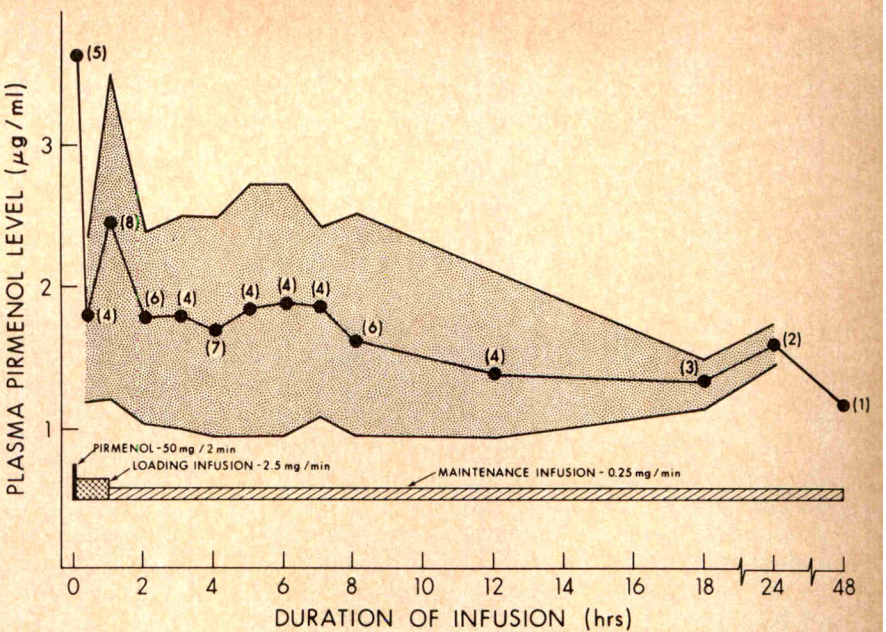

FIGURE 2. Mean and range of plasma pirmenol concentration are shown during the concentration-maintaining intravenous infusion. Mean values were determined from 1 infusion for each of the 8 subjects. Number of subjects for whom data were available at each time is shown in parentheses. Range of plasma pirmenol levels represent extremes observed during all 12 infusions (4 subjects received both a 4-hour infusion on double-blind study days and an open-label infusion for ≥8 hours).

Pirmenol assay: Blood samples were placed in heparinized glass tubes and immediately centrifuged. The plasma was separated, frozen, and stored at −20°C until assay. Pirmenol concentration in plasma was measured using a previously described high performance liquid chromatographic technique.[7] Efficiency of the extraction technique was 70 ± 1.5%. The method was sensitive to approximately 0.1 μg/ml of pirmenol with a coefficient of variation of 7%.

Statistical analysis: For the analysis of drug efficacy during the double-blind, crossover protocol, the quantity R = mean log (PVBs per half-hour + 1) for each half-hour of the 4-hour treatment period (8 half-hour periods) − mean log (PVBs per half-hour + 1) of the average for the 30-minute control periods was computed for each of the 2 study days for each subject. R measures the response during the infusion period with respect to baseline for that day. The difference R (pirmenol) minus R (placebo) was calculated for each subject and the differences were tested for their median being zero using the Wilcoxon signed-rank test. This analysis controls for day-to-day variability in PVB frequency.

Differences in blood pressure, heart rate, and electrocardiographic intervals were also compared using the Wilcoxon signed-rank test.

Results

Effect of pirmenol on PVB frequency: During the double-blind protocol, 1 of the 6 subjects failed to meet the inclusion criteria of at least 1 PVB/min during both control periods and was excluded from analysis of efficacy. In the remaining 5 patients, the effect of pirmenol was apparent within minutes after the priming injection. Average PVB frequency was reduced 93 ± 6% during the infusion of pirmenol (Fig. 1). Placebo infusion was associated with a slight increase in PVB frequency (+7 ± 7%). This difference was statistically significant ($p = 0.03$, $n = 5$). Four of 5 subjects had ≥90% reduction in PVBs throughout the infusion. One subject had nearly complete suppression of PVBs for the first 2 hours of pirmenol infusion and then had a return of ectopy; in this subject, PVB frequency was reduced 48% for the 4-hour infusion.

A ≥90% reduction in PVBs persisted for approximately 6 hours after the end of the pirmenol infusion, at which point plasma pirmenol concentration was 0.95 ± 0.24 μg/ml (n = 4).

In 4 subjects who received prolonged pirmenol infusions, PVB frequency was reduced 94 ± 5% during the fourth through the eighth hours of the infusion. Suppression of ectopy was complete and maintained throughout the infusion for the 2 subjects who received pirmenol infusions of 18 and 48 hours.

Plasma pirmenol levels: The 8 subjects received 12 separate infusions of pirmenol for 4 to 48 hours (Fig. 2), including double-blind and open-label study days. Plasma pirmenol levels immediately after completion

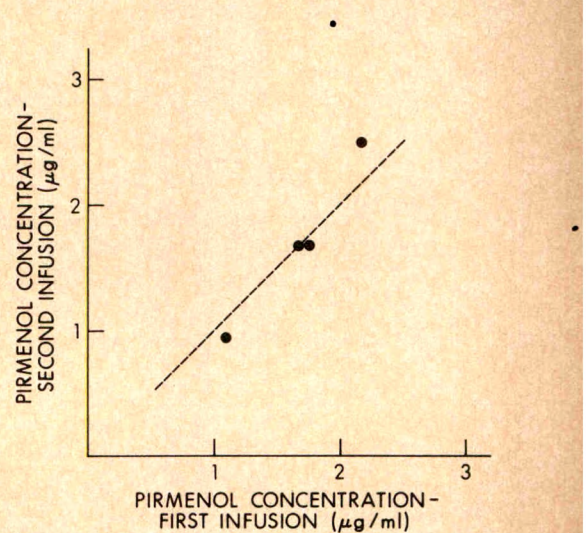

FIGURE 3. Intrasubject variability of plasma pirmenol concentration for the 4 subjects who received 2 separate infusions is shown. Pirmenol concentrations after 4 hours of infusion are compared. The line of identity is also shown.

of the 50 mg bolus injection averaged 3.41 μg/ml but were very variable (range 2.25 to 6.11 μg/ml).

The minimum plasma concentration observed during the rapid loading infusion was 1.20 μg/ml. At the end of the rapid loading infusion, plasma pirmenol concentration averaged 2.43 ± 0.65 μg/ml. Plasma pirmenol concentration during the maintenance infusion remained nearly constant for each subject and ranged from 0.94 μg/ml to 2.75 μg/ml (mean 1.66 ± 0.52 μg/ml) for all subjects and was close to the predicted concentration of 1.75 μg/ml. Four subjects who received a 4-hour infusion during double-blind testing and a more prolonged infusion during open-label testing had very comparable plasma concentrations during both infusions (Fig. 3). The intersubject variation in concentration was not related to differences in subject weight or body surface area.

Effect of pirmenol on blood pressure, heart rate, and electrocardiographic intervals: Table I is a comparison of measured variables during the infusion of pirmenol. Systolic blood pressure, heart rate, and P-R interval were not significantly influenced by pirmenol. There was a slight but statistically significant ($p = 0.03$) increase in diastolic blood pressure during 4-hour infusions. Analysis of the first 2 hours of the infusion separately from the last 2 hours of infusion revealed no progressive increase in diastolic blood pressure during the course of the infusion. Moreover, the increase was not maintained during infusions longer than 4 hours. No subject manifested a clinically important increase in blood pressure.

There were also slight increases in QRS duration and corrected Q-T interval during infusions of pirmenol. Again there was no apparent tendency for progressive prolongation during infusions.

Adverse effects: The 12 infusions in 8 subjects represented 142 hours of pirmenol administration. No subject had any symptoms or adverse effects during infusion. One subject had mild erythema at the infusion site that may have been related to 24 hours of pirmenol infusion.

No laboratory abnormalities or changes in renal, hepatic, or hematologic assessment were associated with pirmenol infusion.

Discussion

In this study, we used a randomized, double-blind, placebo-controlled design to establish that a continuous pirmenol infusion had sustained antiarrhythmic activity in patients with PVBs. Additionally, the infusion regimen produced stable plasma pirmenol levels for up to 48 hours. The antiarrhythmic effect was sustained throughout the longest infusions, indicating a lack of tachyphylaxis to the therapeutic effect of pirmenol. No clinically important toxicity was observed. This demonstration of sustained antiarrhythmic effect and the lack of toxicity suggests that intravenous pirmenol may be an alternative to lidocaine for treatment of ventricular arrhythmias.

Patients enrolled in our study were clinically stable; they did not have symptomatic ventricular tachycardia. However, we believe that these stable patients are an appropriate population for initial clinical testing of new drugs for the treatment of ventricular arrhythmias. Unstable patients with acute myocardial infarction or symptomatic ventricular tachycardia are likely to be less suitable for a carefully controlled clinical trial such as this one with a placebo phase.

Hammill et al[4,5] suggested that 1.0 μg/ml was the minimal therapeutic concentration of pirmenol based on the reappearance of arrhythmia after short-term infusions. A ≥90% reduction in PVBs was observed with plasma concentrations in the range of 0.7 to 2 μg/ml after oral[5] and 1 to 3.8 μg/ml after intravenous administration; no important toxicity was observed. In the present study, the 3-stage infusion regimen is seen to be very effective in rapidly achieving and maintaining stable plasma pirmenol levels from 0.9 to 2.75 μg/ml. Pirmenol did not accumulate during the infusion. The infusion regimen was designed for maximum simplicity. The first stage was a 50 mg bolus, which was delivered by a hand-held syringe. The second stage (2.5 mg/min for 1 hour) was exactly 10× the third stage (0.25 mg/min continued indefinitely). Our present study extends the safety of pirmenol at therapeutic levels for up to 48 hours. No symptoms were reported by any patient during infusion and no important changes were observed on physical examination or extensive laboratory profiles.

Diastolic blood pressure increased significantly during infusions, perhaps due to the suppression of PVBs and a consequent increase in effective heart rate. Two subjects had diastolic pressures >90 mm Hg (but <100 mm Hg), but the increase in diastolic pressure was neither progressive nor maintained during prolonged infusions. A recent hemodynamic study of pirmenol

TABLE I Effect of Pirmenol and Placebo Infusion on Blood Pressure, Sinus Rate, and Electrocardiographic Intervals

	Control	Placebo Infusion	Control	Pirmenol Infusion
Systolic blood pressure (mm Hg)	135 ± 18	137 ± 21	130 ± 16	136 ± 18
Diastolic blood pressure (mm Hg)	76 ± 7	76 ± 5	74 ± 6	86 ± 8*
Sinus rate (beats/min)	74 ± 13	72 ± 7	70 ± 10	73 ± 10
P-R interval (s)	0.172 ± 0.021	0.177 ± 0.023	0.172 ± 0.024	0.179 ± 0.021
QRS duration (s)	0.083 ± 0.010	0.084 ± 0.010	0.081 ± 0.014	0.090 ± 0.007*
Corrected Q-T interval (s)	0.428 ± 0.048	0.433 ± 0.043	0.425 ± 0.032	0.470 ± 0.042*

* $p \leq 0.05$.

Data were obtained during double-blind infusions of pirmenol and of placebo ($n = 6$). Control data are the average of measurements during the 1-hour control period. Infusion data represent measurements obtained during the infusion period. The corrected Q-T interval was calculated as Q-T/$\sqrt{}$ R-R interval.

concluded that pirmenol was unlikely to cause important myocardial depression, at least in patients with normal left ventricular function.[8]

Pirmenol infusions prolong QRS duration and corrected Q-T interval approximately 10%. This has been observed in previous human studies[4,5] and is consistent with the local anesthetic action of pirmenol observed in isolated dog Purkinje fiber preparations.[1] Importantly, prolongation of the QRS duration and Q-Tc interval were not progressive during extended infusions.

In conclusion, the present study demonstrates that our 3-stage intravenous regimen satisfactorily achieved and maintained plasma pirmenol levels that suppressed PVBs with no toxicity. Pirmenol is a promising agent that warrants further evaluation in other types of arrhythmias.

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Current Physiologic Pacemakers: A Serious Problem With a New Device

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Twenty adults underwent implantation of an automatic (DDD) pacemaker (Medtronic model 7000, Versatrax I) for treatment of symptomatic bradyarrhythmias. Only 9 patients had optimal DDD mode pacing during 78 paced months. In 3 patients, the DDD mode was changed to atrioventricular (AV) sequential (DVI) early because of risk imposed by sustained tachycardia upon underlying myocardial ischemia. The remaining 8 had had tachycardia due to pacemaker reentry, and 7 had neurologic and cardiovascular symptoms. DDD pacing was abandoned in 5 when reentry could not be interrupted by digitalis administration or reprogramming. Three continue to be paced in DDD mode despite intermittent reentrant tachycardias, with digitalis diminishing episodes of reentry in only 1. Mean ventriculoatrial conduction time was 229 ± 34 ms. Reentrant pacemaker tachycardia developed in 7 of 12 with normal or nearly normal AV conduction, but in only 1 of 5 with complete heart block. Preimplantation electrophysiologic study did not reliably detect and initial postoperative Holter monitoring did not predict reentrant tachycardia. The risk of reentry caused by a short, fixed atrial refractory period combined with the high occurrence of slow retrograde AV conduction, particularly in patients with normal or nearly normal anterograde conduction, renders the Versatrax I and other similar pacemakers unsuitable for DDD mode pacing in many patients.

Properly timed atrial systole maintains reduced filling pressure, which facilitates venous return, augments ventricular filling, assists closure of atrioventricular (AV) valves, and thereby improves ventricular function. Typically, the increment in cardiac output achieved by preserving AV synchrony over a rate-matched, paced ventricular rhythm (lacking synchronous atrial systole) approaches 20%.[1–7]

Fully automatic pacemakers are indicated in AV block with normal sinus nodal function. Their use may be indicated in persons requiring atrial demand (AAI), P-synchronous (VDD), or AV sequential (DVI) pacing.[8] Because of the necessity for atrial-sensing and ventricular-triggering functions, the pacemaker can behave as the efferent limb of a reentrant tachycardia if retrograde atrial excitation initiated by ventricular pacing is sensed by the atrial electrode. The ensuing ventricular stimulus is premature and recurrent retrograde conduction causes a sustained tachycardia.

This report reviews early results in 20 patients who received fully automatic pacemakers for treatment of symptomatic bradyarrhythmias. The high frequency of reentrant tachycardias observed supports the importance of modification of currently available automatic pacemakers to minimize the threat of sustained, pacemaker-mediated tachycardia.

Methods

Twenty adults underwent implantation of a fully automatic pacemaker (Medtronic model 7000, Versatrax I) between December 1, 1981, and November 30, 1982. The Versatrax I is a multiprogrammable, lithium-powered, dual-chamber device which employs a unipolar electrode in atrium and ventricle. The hermetically sealed case serves as the indifferent electrode for both leads. Externally programmable features include mode (VVI, DVI, or DDD), AV interval, rates, rate limits, and independent adjustment of each electrode's pulse width and sensitivity. However, the atrial refractory period measured from the ventricular stimulus or a ventricular-sensed event is fixed at 155 ms.

Eight patients underwent preimplantation electrophysiologic studies to define sinus nodal and conduction system

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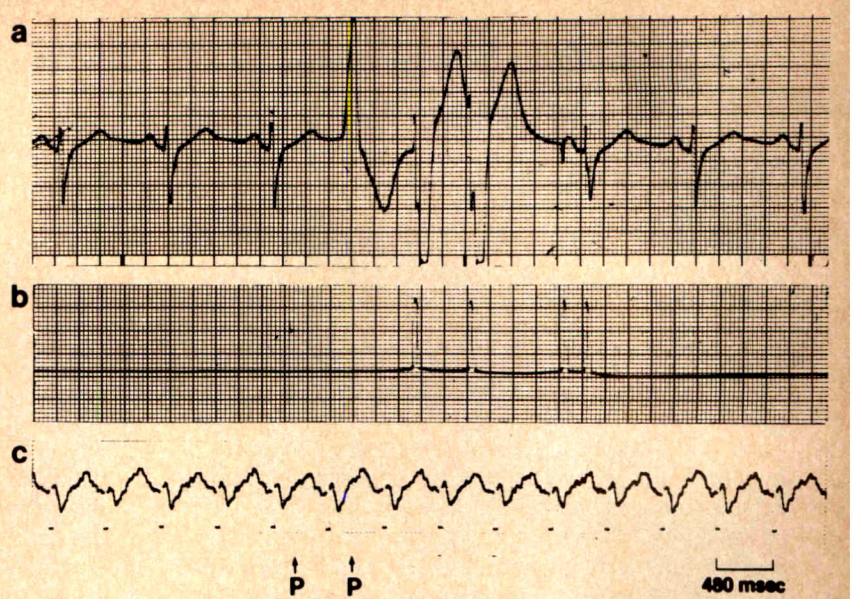

FIGURE 1. Fifty-two-year-old man (Group II) after pacemaker implantation (see text). **a,** early postimplantation Holter (first channel). Three normal sinus beats: ventricular premature beat followed by 2 paced ventricular beats at R-R interval of 480 ms (programmed upper rate limit). Patient recovers normal sinus rhythm spontaneously after single AV sequential (DVI) paced cycle. **b,** early postimplantation Holter timing trace (second channel). Single artifacts are ventricular stimuli in response to sensed reentrant "P"-waves at programmed upper rate limit. Paired artifacts of DVI cycle are atrial and ventricular separated by programmed AV delay of 200 ms. **c,** eight days after implantation telephone surveillance electrocardiogram which demonstrates sustained P-synchronous ventricular-paced tachycardia at 125 ppm (programmed upper rate limit). **P** marks retrograde P-wave approximately 200 ms after the ventricular artifact.

function. An attempt also was made to detect retrograde right ventricle-to-right atrium conduction by pacing from several sites in the right ventricle and recording from the right atrial appendage.

All 20 patients had a ventricular electrode (Medtronic model 6971) and an atrial electrode (Medtronic model 6991U) inserted under fluoroscopic control using standard implantation techniques. Electrode impedance of 300 to 700 ohms was ascertained. Filtered and unfiltered intracavitary electrograms were recorded from the electrodes to assure adequate voltage for the pacemaker-sensing amplifiers. Voltage threshold for capture was measured as a function of pulse duration in order to guarantee myocardial stimulation.

Ambulatory electrocardiographic (ECG) monitoring was employed in all patients for 18 to 39 hours after implantation to assure proper pacemaker function. A 2-channel pacemaker recording unit (Del Mar Avionics model 448), which recorded an ECG lead on 1 channel and the pacemaker stimulus artifacts on the other channel, was routinely used in interpreting electrical events (Fig. 1, a and b). Three atrial leads became dislodged and were successfully repositioned. All patients were discharged without surgical complications and were followed up in our telephone surveillance clinic. Inpatient and outpatient monitoring was conducted with particular attention to the identification of a supraventricular tachycardia in which the pacemaker programmed in DDD mode formed 1 limb of a reentrant loop. Such a loop would be closed by the atrial amplifier sensing recurrent ventriculoatrial (VA) conduction that occurs >155 ms from the ventricular event.

Reentry induced by a pacemaker functioning in DDD mode was defined as a regular sustained tachycardia at a rate equal to the programmed upper rate limit. The instantaneous cessation of this tachycardia, either by reprogramming the pacemaker to a lower rate without atrial sensing (VVI or DVI mode) or by applying a magnet over the pulse generator and converting to DVI mode temporarily, further identified the arrhythmia as pacemaker-induced. The ECG pattern of pacemaker-induced tachycardia is characterized by the pacemaker functioning normally in a P-synchronous manner with retrograde P-waves (sensed), followed by a paced ventricular beat triggered by the sensed atrial event at the preset upper rate limit. VA conduction times were measured from the ventricular artifact to the beginning of the retrograde P-wave. P-wave duration to point of sensing was not measured.

TABLE I Summary of Initial Clinical Experience in 20 Patients Receiving Versatrax I Pacemakers

Group	First Paced DDD (n)	With Retrograde Reentry (n)	Retrograde Times (ms)*	Now Paced DVI (n)
I	10	5	180, 220, 240, 260, 280	6
II	5	2	200, 200	2
III	5	1	250	0
Totals	20	8		8

* Mean retrograde conduction time 229 ± 34 ms.
Group I = sinus bradycardia with normal AV conduction; Group II = sinus rhythm with prolonged AV conduction; Group III = complete heart block.

Results

Table I summarizes our initial clinical experience. Indications for artificial cardiac pacing in all patients were symptomatic bradyarrhythmias characterized by sinus bradycardia with normal AV conduction in 10 (Group I), sinus rhythm with prolonged AV conduction in 5 (Group II), and complete heart block in 5 (Group III). In addition, of the 5 Group II patients, 4 had ≥1 syncopal episodes, 2 had hypertrophic cardiomyopathy, 1 had dilated cardiomyopathy, and 2 had abnormal sinus nodal function. All 20 patients have been followed from 2 to 12 months for a total of 78 months.

In Group I, 5 had pacemaker-mediated reentrant tachycardias. Retrograde conduction times ranged from 180 to 280 ms. Digitalis controlled reentrant tachycardia in 1 but not in another. Reduction of the upper rate limit eliminated the symptoms but not the reentrant tachycardia itself in a third. DDD mode was abandoned in 3 because both reprogramming and drug intervention failed to control symptomatic reentrant rhythms. DVI mode was selected early in 3 others because of the risk

imposed by reentrant tachycardias upon underlying ischemic heart disease. Of the 10 Group I patients, only 4 continued to have DDD mode pacing.

Two Group II patients suffered reentrant rhythms that could not be controlled by either reprogramming or drugs; DDD pacing was abandoned in these patients. Retrograde times were 200 ms in both instances (Fig. 1). All Group III patients have had successful DDD mode pacing. One, who is asymptomatic, has intermittent episodes of pacemaker-mediated reentrant tachycardia with a retrograde time of 250 ms. The mean retrograde conduction time in the 8 patients from Groups I, II, and III who manifested reentrant rhythms was 229 ± 34 ms.

Figure 1 illustrates an instance of pacemaker-initiated reentrant tachycardia in a 52-year-old man (Group II) who presented with a recent history of recurrent syncope. Hypertrophic cardiomyopathy was previously diagnosed and several 24-hour ECG recordings demonstrated frequent multifocal ventricular premature beats without coupling or runs of ectopic rhythm. An electrophysiologic study demonstrated an H-V interval of 115 ms. Programming extrastimuli at different coupling intervals in the right ventricle failed to elicit retrograde conduction. Although the frequency of ventricular premature beats was controlled with propranolol and disopyramide, syncope recurred. No ECG data were ever obtained during syncope. A Versatrax I pacemaker was implanted. Figure 1a, an excerpt of the early postimplantation Holter recording, illustrates 1 of several brief and self-limited episodes of pacemaker reentry at the programmed upper rate limit (125 pulses/min). The patient was discharged from the hospital with his previous drug regimen and the addition of digitalis to block the retrograde conduction. Eight days after implantation, the patient contacted the pacemaker surveillance clinic complaining of continuous palpitations, overwhelming weakness, and dizziness. The telephone surveillance electrocardiogram (Fig. 1c) revealed a sustained P-synchronous ventricular-paced tachycardia at the pacemaker's programmed upper rate limit. Reprogramming the pacemaker to DVI mode relieved the tachycardia and the patient's complaints. Digitalis was discontinued. After 6 months of observation, syncope has not recurred and the patient has returned to work.

Neither preimplantation electrophysiologic study nor postimplantation ambulatory ECG monitoring predicted the occurrence of pacemaker-mediated tachycardias. In 8 of the original 20 patients, attempts to elicit retrograde conduction during electrophysiologic study performed without sedation or parasympathetic blocking agents failed before pacemaker implantation. Nevertheless, reentrant supraventricular tachycardia with the pacemaker acting as 1 limb of the reentrant loop occurred in 2. Ambulatory ECG monitoring detected reentrant rhythms immediately in only 3, and from 3 days to 3 months after implantation in the remaining 5. Four of the 5 with late detection of reentry had no evidence of supraventricular tachycardia during ambulatory ECG recordings immediately after implantation.

Seven of the 8 patients with reentrant tachycardia had neurologic and cardiovascular symptoms at the time the arrhythmia was detected, including postural dizziness, peripheral weakness, and dyspnea at rest or with minimal exertion. Serious complications were 2 cases of pulmonary edema and 1 case of unstable angina pectoris due to unrelenting tachycardia. Reprogramming to slower rates in DVI mode partially relieved the symptoms and signs of the complications in all 3 cases.

Discussion

A pacing system which restores AV synchrony over a physiologic range of rates was described by Funke and Herpers in 1978.[9] The Versatrax I, which is a more advanced version of the Funke device, is described as a "fully automatic" (DDD or DD-T/I) atrial synchronous, atrial demand, ventricular demand device. This pacemaker can stimulate the atrium only in sinus bradycardia without block (AAI mode), atrium and ventricle sequentially in sinus bradycardia with block (DVI mode), or P-synchronously in block with normal sinus nodal function (VDD or VD-T/I mode). It can also remain in standby mode during normal sinus rhythm. Ventricular inhibition minimizes the chance of competitive ventricular rhythms. Operation shifts logically and automatically from 1 mode to another, on a beat-to-beat analysis of the underlying rhythm by the device's logic circuitry. A fixed atrial-sensing refractory period after a ventricular event of 155 ms was tacitly assumed to be an adequate time to filter out most rapidly conducted retrograde P-waves capable of initiating an undesirable, pacemaker-induced tachycardia. A prolonged atrial refractory period appeared to be undesirable because of limitations necessarily imposed upon the maximum atrial tracking rate of the pacemaker in response to a physiologic sinus tachycardia.[10,11]

In 1981, Morley et al[10] emphasized the importance of recognizing retrograde AV conduction in patients selected for physiologic pacing systems. Of their patients with persistent or intermittent high-grade block, 32% had retrograde conduction during electrophysiologic study. Of those with no evidence of AV conduction abnormality, 90% had retrograde P waves. Mean retrograde time was 206 ± 42 ms with a range of 160 to 330 ms, a retrograde time very similar to the 229 ± 34 ms of our study. This study warned of the possibility of reciprocating tachycardias in pacing systems with short atrial refractory periods. Our results corroborate Morley's findings. We have found that pacemaker-induced supraventricular tachycardia is a common problem among patients without complete heart block but is infrequent in the patients with complete anterograde AV block (Table I).

Our clinical experience reveals that we cannot rely upon detection of retrograde conduction during electrophysiologic study or the absence of reciprocating rhythms on routine, early postimplantation ambulatory ECG recording to prevent real or potential clinical complications. Moreover, we cannot eliminate the possibility of triggering reentry after retrograde con-

duction caused by random ventricular ectopic beats.[11–13] During our more recent experience, the pacemakers of 3 patients were intentionally programmed to DVI mode because of potential risk imposed by a pacemaker-induced tachycardia upon underlying ischemic heart disease.

Several reports have cited cases of complex rhythm disorders associated with pacemakers capable of synchronizing ventricular systole with atrial activation.[14–16] Other data from electrophysiologic studies in man illustrate >90% incidence of retrograde conduction as a result of ventricular extrasystoles. Retrograde conduction times >390 ms were common. Shorter VA conduction times were only infrequently associated with reciprocal rhythms, whereas longer times frequently induced the reentry mechanisms.[12] Our clinical data illustrate retrograde conduction times (229 ± 34 ms) within the range often associated with reentrant tachycardias.

The occurrence of 3 potentially fatal complications due to pacemaker-induced tachycardia suggests that we should carefully observe Morley's warning[10] and eliminate the possibility of slow retrograde conduction before programming the Versatrax I to operate in DDD mode. Ideally, the investigation for retrogrades could be performed at the time of atrial and ventricular electrode insertion. Because of our lack of success in demonstrating retrograde conduction, we have debated the value of pursuing any electrophysiologic study before using the Versatrax I. We should have anticipated the high incidence of retrograde conduction in Group I. These patients with normal anterograde conduction would have responded well to atrial demand pacing (AAI). Establishing a pulse generator AV delay well in excess of their normal AV conduction times should have effectively caused the Versatrax I to function automatically in AAI mode in these patients. The expected result was not achieved in any Group I patient who had reentry. Some of our records suggest that retrograde conduction followed a random ventricular extrasystole which then entrained the sustained P-synchronous pacemaker response at the programmed upper rate limit (Fig. 1a).

We must conclude that a pulse generator atrial refractory period of 155 ms renders the Versatrax I very vulnerable to potentially dangerous reciprocating tachycardias. Such a device is unsatisfactory for DDD pacing in many patients, particularly those with sinus bradycardia and normal or nearly normal AV conduction. Among the theoretical pulse generator-based algorithms for recognizing and managing sustained pacemaker reentry, we believe that prolonging the atrial refractory period to encompass the expected mean retrograde conduction time is the least complex and potentially most effective choice. While a longer refractory period imposes an upper limit upon the maximum physiologic atrial rate which would guarantee 1-to-1 atrial synchronous, ventricular pacing, the threat of reciprocating rhythms due to slow retrograde conduction will be significantly reduced or eliminated. The implied decrease in maximum atrial tracking rate would not seriously compromise the daily routine of the majority of our patients who might otherwise benefit significantly from DDD mode pacing. The often intermittent nature of slow reentry renders electrophysiologic study before implantation and ambulatory ECG after implantation unreliable as predictors of this most serious complication of physiologic pacing systems. External programming control of the atrial refractory period may obviate the need for pursuing a diagnosis of retrograde conduction before implantation. A controllable atrial refractory period will allow more liberal use of physiologic pacing systems in the treatment of symptomatic bradyarrhythmias.

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Left Ventricular Function at Rest and During Exercise in Congenital Complete Heart Block: A Radionuclide Angiographic Evaluation

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This study evaluates intrinsic cardiac performance during upright exercise in patients with congenital complete heart block. Left ventricular ejection fraction and volume were measured at rest and peak upright exercise with radionuclide angiography in 5 patients aged 11 to 39 years with congenital complete heart block: 4 were in New York Heart Association class I and 1 was in class II. The resting cardiac output was maintained at a normal level by an increase in end-diastolic volume rather than by a decrease in end-systolic volume. The left ventricular ejection fraction was normal at rest in all patients, but an abnormal response to exercise was noted in 3 patients. There was no appreciable change in the end-diastolic volume during exercise. Thus, patients with congenital complete heart block utilize the Starling mechanism to maintain normal resting cardiac output, but the response to exercise is usually abnormal even in the absence of symptoms.

Congenital complete heart block (CHB) is uncommon, occurring in 1:5,000 to 1:20,000 live births.[1,2] Several previous studies[3–7] have described the exercise tolerance and changes in heart rate, cardiac output, and blood pressure during exercise in a few patients, but changes in ventricular volume and function have not been described. Herein we report left ventricular (LV) ejection fraction (EF) and volume at rest and during upright exercise in 5 patients with congenital CHB.

Methods

Five patients with congenital CHB, 4 female and 1 male between the ages of 11 and 39 years, were studied (Table I). Criteria[1,8] for diagnosis of congenital CHB included (1) CHB noted before birth or during infancy; (2) independence of atrial and ventricular rates; (3) ventricular rate slower than atrial rate; and (4) absence of history of other factors that may cause CHB after birth.

The electrocardiograms revealed QRS complexes of normal duration in 4 patients and prolonged QRS duration in 1 patient (Case 5). One patient (Case 4) had a maternal history of systemic lupus erythematosus,[9] and also trivial aortic regurgitation. The remaining 4 patients had no associated cardiac abnormalities. No patient was receiving cardioactive medication; 4 patients were in New York Heart Association functional class I and 1 patient (Case 4) was in class II. No patient had electrocardiographic criteria for LV hypertrophy. A systolic ejection murmur (left sternal border and grade 1/6) was heard in 4 patients (Cases 2 to 5).

Exercise testing: Exercise studies were performed with the patient in the upright position, using a variable-load bicycle ergometer (Quinton Instruments). The method of exercise testing has been described.[10] The exercise endpoints were dyspnea (Patients 1 and 3); fatigue (Patients 2 and 4) and dizziness (Patient 5). First-pass radionuclide angiograms were obtained at rest and peak exercise by means of a computerized multicrystal gamma camera (Baird-Atomic System-77). The LVEF, end-diastolic volume, and end-systolic volume were measured according to a previously described method from this laboratory.[10,11] All volumes were subsequently indexed by dividing the measurement by the body surface area in square meters.

Results

The cardiac index at rest was normal in 4 patients. The patient with reduced cardiac index (Patient 5) had the smallest end-diastolic volume (Table I). All 5 patients had normal EF but increased end-diastolic volume indexes at rest (limits of normal values in our laboratory are $\geq 50\%$ and < 100 ml/m^2, respectively). Thus,

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TABLE I Resting and Exercise Hemodynamics in 5 Patients With Congenital Complete Heart Block

Case	Age (yr) & Sex	AR		VR		BP		EF		EDVI		ESVI		SVI		CI		Ex Duration (min)
		R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	
1	24F	83	176	45	64	120/80	165/60	64	63	172	181	62	66	110	114	4.9	7.0	5.9
2	11F	94	136	71	101	110/80	140/70	70	79	136	128	40	28	95	100	6.8	10.1	9.0
3	39F	81	150	62	95	120/80	180/90	68	49	125	123	41	63	83	60	5.1	5.7	6.0
4	13F	93	150	38	62	110/80	120/90	53	50	165	175	87	91	87	91	3.3	5.6	4.5
5	25M	73	120	40	75	130/70	190/80	52	64	114	106	55	38	60	68	2.2	4.4	13.0

AR = atrial rate (beats/min); BP = blood pressure (mm Hg); CI = cardiac index (liters/min/m^2); EF = ejection fraction (%); EDVI = end-diastolic volume index (ml/m^2); ESVI = end-systolic volume index (ml/m^2); Ex = exercise; R = resting; SVI = stroke volume index (ml/m^2); VR = ventricular rate (beats/min).

the resting cardiac output is maintained normal by an increase in end-diastolic volume rather than a decrease in the end-systolic volume. During exercise, the cardiac index increased in all patients. The smallest change was observed in the oldest patient in the group (Patient 3). Only 1 patient was able to double the cardiac output. The EF increased by at least 5% (absolute units and normal response) in 2 patients (Cases 2 and 5), remained unchanged (<5% change) in 2 patients (Cases 1 and 4), and decreased in 1 patient (Case 3). The patient with a decrease in EF during exercise was the oldest patient in the group. The 2 patients with normal EF responses to exercise had greater exercise tolerance than the remaining patients. These 2 patients had a decrease in end-systolic volume during exercise, but the remaining 3 patients had an increase. There was no appreciable change in the end-diastolic volume with exercise in all 5 patients.

Discussion

There are few studies describing hemodynamic abnormalities during exercise in patients with congenital CHB. These studies, in a total of 8 patients, described the changes in cardiac output, heart rate, and stroke volume. Studies in larger numbers of patients have been reported describing the changes in atrial and ventricular rates.[3–7,12–15]

Our results showed that the cardiac output increased during exercise in patients with congenital CHB, and that this increase was due to an increase in ventricular rate. Although the cardiac output increased in all 5 patients with exercise, only 1 patient was able to double the cardiac output. The resting cardiac output was maintained in these patients, despite the slow ventricular rate, by LV dilation. This finding is in agreement with other clinical and experimental studies in which the cardiac volume was measured with roentgenography.[3,16] One of the 5 patients (Case 5) had reduced cardiac output at rest; this patient also had the smallest end-diastolic volume index. No patient had an increase in end-diastolic volume during exercise. The LVEF at rest was normal in all 5 patients; however, an abnormal response to exercise was observed in 3 patients. The worst LV function during exercise was observed in the oldest patient in the group (Patient 3), and this was the only patient who was in functional class II; this patient had no historic evidence or risk factors to suggest the presence of associated coronary heart disease. The remaining patients were asymptomatic.

The reason(s) for abnormal cardiac reserve function during exercise in some patients with congenital CHB is not clear but may be attributable to chronic volume overload, similar to that observed in patients with chronic aortic regurgitation,[10,17–19] and this abnormality may be more pronounced in the older patient.[17] In this and other studies,[3–5] the exercise capacity was not related to the cardiac output. Taylor and Godfrey[4] suggested increased peripheral extraction of oxygen and the ability to tolerate low venous oxygen tensions as possible mechanisms to maintain a normal working capacity in such patients.

The contribution of atrial activity to ventricular filling and cardiac output is not clear from our study. The patient with the lowest atrial rate at rest and exercise had the lowest cardiac output at rest and exercise. However, this patient (Case 5) also had the smallest end-diastolic volume.

The hemodynamic responses to exercise in patients with congenital CHB are therefore entirely different from those observed in normal subjects, who increase their cardiac output during upright exercise by increases in heart rate and stroke volume and who also have increases in EF, a slight increase in end-diastolic volume, and a decrease in end-systolic volume.[10,20,21]

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Idiopathic Paroxysmal Ventricular Tachycardia With a QRS Pattern of Right Bundle Branch Block and Left Axis Deviation: A Unique Clinical Entity With Specific Properties

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Electrophysiologic evaluation before and after the serial administration of verapamil, lidocaine, propranolol, and procainamide was undertaken in 4 young, asymptomatic patients with recurrent, sustained ventricular tachycardia (VT). No patient had obvious organic heart disease. The electrocardiogram during sinus rhythm showed S-T depression and T-wave inversion over the inferior and lateral precordial leads in 3 patients. QRS morphologic characteristics during episodes of VT showed a pattern of right bundle branch block and left axis deviation. In all 4 patients, VT could be both induced and terminated with electrical stimulation. Verapamil terminated VT and prevented the induction o sustained VT in 3 patients, and markedly slowed the rate of VT in 1 patient. Procainamide effectively prevented the induction of sustained VT in 2 patients and although ineffective in preventing induction ir 2 patients, it slowed the rate of tachycardia in both. Lidocaine and propranolol did not prevent the induction of VT in any patient. These findings suggest that slow-response tissues may be involved in the genesis of VT in these patients, and that VT in these patients may represent a unique clinical entity with distinct electrocardiographic, electrophysiologic, and electropharmacologic properties.

Sustained ventricular tachycardia (VT) usually occurs in patients with organic heart disease, particularly in patients with a myocardial aneurysm subsequent to myocardial infarction.[1–4] Reentry is the most common mechanism of VT in these patients.[1,5] Nonetheless, sustained VT may occur in patients without demonstrable organic heart disease,[1,2,6,7] and mechanisms other than reentry may be responsible for VT in some.[6,7] In this study, we report on 4 young, asymptomatic patients with recurrent, sustained VT but without obvious organic heart disease. Their electrocardiographic manifestations of VT, electrophysiologic behavior, and pharmacologic responses were unique.

Methods

This study consisted of 4 young, asymptomatic patients, 2 female and 2 male, aged between 24 and 35 years (mean 27), with electrocardiographic documentation of recurrent, sustained VT manifesting a QRS pattern of right bundle branch block (BBB) and left axis deviation (LAD). In 3 patients the spontaneous episodes of VT could be terminated by intravenous administration of 5 to 10 mg of verapamil during emergency room visits.

All electrophysiologic studies were performed in the postabsorptive, nonsedated, and supine state after having obtained written informed consent. A #6 quadripolar electrocatheter was percutaneously introduced into the right femoral vein, advanced to the right atrium, and positioned across the tricuspid valve. The distal 2 electrodes were used for right ventricular stimulation, whereas the proximal 2 electrodes were used for His bundle recording. A #7 hexapolar electrocatheter was introduced into a right antecubital vein through a small incision and advanced to the right atrium and then into the right ventricle. The distal 2 electrodes were used for right ventricular pacing, the middle 2 electrodes for recording of the right atrial electrogram, and the proximal 2 electrodes for right atrial stimulation. Surface electrocardiographic leads and intracardiac electrograms were simultaneously recorded on a multichannel oscilloscopic photographic recorder (Electronics for Medicine VR-16, White Plains, New York) at a paper speed of 100 mm/s. Electrical stimuli of 2 ms duration approximately twice the diastolic threshold were provided by a programmable digital stimulator (DTU PG 100, manufactured by Bloom and Associates, Narberth, Pennsylvania).

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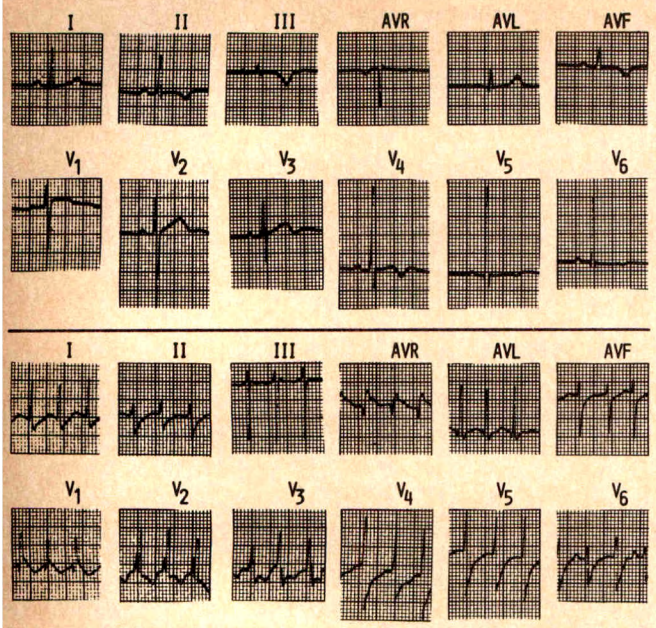

FIGURE 1. Electrocardiograms in case 1 showing ST-T changes over leads II, III, aVF, and V_4 through V_6 during sinus rhythm (**upper panel**) and a QRS pattern of right BBB and LAD occurring during a spontaneous episode of tachycardia (**lower panel**).

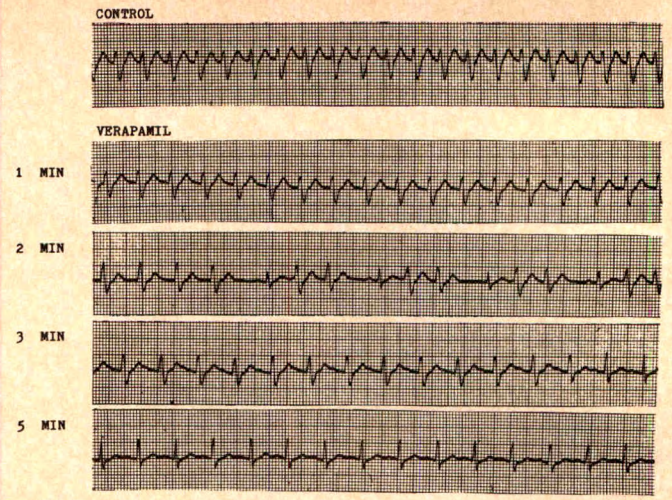

FIGURE 2. Rhythm strips of the monitor lead in case 3 showing termination of a spontaneous episode of VT after a bolus of 5 mg of verapamil. The rate of VT was 190 beats/min before verapamil (**first panel**) and slowed to a rate of 150 beats/min within 1 minute after the administration of verapamil (**second panel**). Intermittent sinus capture was noted within 2 minutes (**third panel**), whereas sinus capture with decreasing degree of fusion occurred within 3 minutes (**fourth panel**). Sinus rhythm was resumed within 5 minutes after verapamil (**fifth panel**).

Anterograde and retrograde conduction properties were evaluated by atrial and ventricular incremental pacing and extrastimulus testing techniques. Incremental atrial pacing was performed to the paced cycle length that induced second-degree block proximal to the His bundle recording site. Atrial extrastimulus with single or double premature stimulations was coupled to the sinus cycle length and an atrial driven cycle length. Incremental ventricular pacing was performed up to a paced cycle length of either 250 or 230 ms. Ventricular extrastimulus testing with single or double premature stimulations was coupled to the sinus cycle length and a ventricular driven cycle length.

After the control study, sustained VT was induced. An intravenous bolus of 5 mg of verapamil was given under continuous electrocardiographic monitoring. Regardless of whether or not termination of VT occurred, a second bolus of 5 mg of verapamil was given 5 minutes later. If spontaneous termination of VT was noted, the electrophysiologic study was repeated. Otherwise, an additional bolus of 5 mg of verapamil was repeated every 5 minutes either until VT was terminated or a total dose of 20 mg of verapamil had been administered, at which time VT was terminated with electrical stimulation and the study repeated. After this initial evaluation, the quadripolar catheter was removed and the tip of the hexapolar catheter was positioned at the right ventricular apex and secured for serial subsequent studies. On day 2, sustained VT was induced and 2 boluses of lidocaine (1 mg/kg) were administered with a time interval between doses of 5 minutes. If VT failed to terminate spontaneously within 10 minutes after the second bolus, it was terminated with electrical stimulation and the study repeated. On day 3, sustained VT was induced and intravenous propranolol (0.1 mg/kg) was administered. If VT did not terminate within 15 minutes of the dosage administration, it was terminated with electrical stimulation and the study repeated. On day 4, the patients were treated with oral procainamide 750 to 1,000 mg every 4 hours and the study repeated 2 hours after the sixth dose.

Conduction intervals and refractory periods are defined and measured as previously described.[8] The diagnosis of the VT was confirmed during electrophysiologic study by the demonstration of complete and incomplete atrioventricular dissociation, the occurrence of capture and fusion beats, and the demonstration of no His bundle potential preceding each QRS complex during the tachycardia. Reentry using a nodoventricular connection or a fasciculoventricular connection was excluded.[9]

TABLE I Induction of Ventricular Tachycardia (VT) Before and After Drugs

	Control			Verapamil					Lidocaine		
Case	CL-VT (ms)	RVP* Induction	VEST† Induction	Termination of VT§	CL-VT (ms)¶	Ability to Sustain	RVP* Induction	VEST† Induction	Termination of VT	CL-VT (ms)	Ability to Sustain
1	320	280–230	280–230	0	420	+	500–260	410–390	0	360	+
2	330	300	330–230‡	+	430	0	430–300	310–280‡	0	320	+
3	330	330–280	330–290	+	(−)	(−)	460–360‡	0	0	350	+
4	430	460–300	300–240	+	(−)	(−)	(−)	(−)	+	390	0

* Range of paced cycle lengths that induced VT (in ms).
† Range of coupling interval that induced VT (in ms).
‡ Induction of only 1 or 2 premature ventricular complexes.

Results

Clinical characteristics (Fig. 1 and 2): All 4 patients presented with a history of palpitations ranging from 3 to 12 years with episodes lasting from 10 minutes to 3 days. The frequency of attacks ranged from 3 per 12 years to 8 per year. No patient had obvious heart disease on physical examination, chest X-ray, echocardiogram, cardiac catheterization, and coronary angiography. In 3 patients multiple electrocardiograms taken during sinus rhythm showed S-T depression and T-wave inversion over leads II, III, and aVF, and in the lateral precordial leads (Fig. 1, upper panel). The electrocardiogram was normal in 1 patient (case 3).

The electrocardiograms recorded during spontaneous episodes of VT showed a QRS pattern of right BBB and LAD in all 4 patients (Fig. 1, lower panel). The QRS duration was 0.10 second in 2 patients and 0.12 second in 2 patients. The frontal QRS axis was between −60° and −100°. The rate of tachycardia ranged from 150 to 200 beats/min. Alternation of the cycle length of the VT was observed in 1 patient (case 1). In 3 patients VT was always terminated within a few minutes after the intravenous administration of 5 to 10 mg of verapamil (Fig. 2), whereas 1 patient (case 1) required cardioversion. In no patient was VT provoked by maximal treadmill exercise.

Induction of tachycardia (Table I and Fig. 3 to 5): Sustained VT identical to spontaneous VT was inducible with electrical stimulation in all patients. During induced VT, complete atrioventricular dissociation was

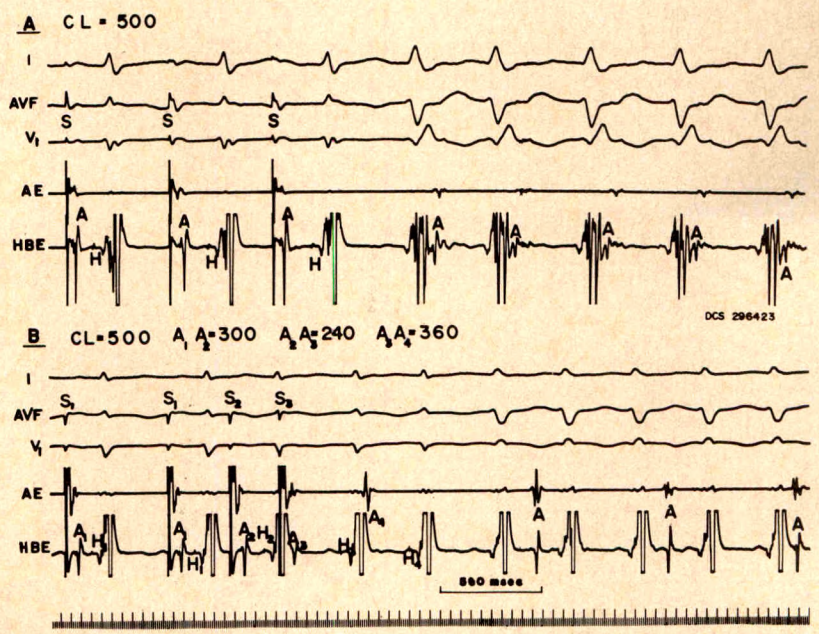

FIGURE 3. Recordings showing the induction of ventricular tachycardia (VT) with rapid atrial pacing in case 4 (**panel A**) and with double atrial premature stimulation in case 2 (**panel B**). In case 4 the VT was induced at an atrial paced cycle length of 500 ms, whereas in case 2 it was induced with 2 atrial premature stimulations at an atrial driven cycle length of 500 ms. The first coupling interval (A_1A_2) was 300 ms and the second coupling interval (A_2A_3) was 240 ms; A_3 induced a premature atrial beat (A_4) which was then followed by the initiation of VT. Note that the initiation of VT in both cases was independent of the development of right bundle branch block or left axis deviation, or both. During VT, intact ventriculoatrial conduction was noted in case 4 and complete atrioventricular dissociation was noted in case 2. A = atrial response to pacing stimulus; A_1 = atrial response to S_1; A_2 = atrial response to S_2; A_3 = atrial response to S_3; A_4 = premature atrial beat after A_3; AE = atrial electrogram recorded from right atrium; CL = cycle length; H = His bundle response to pacing stimulus; HBE = His bundle electrogram; H_1 = His bundle response to S_1; H_2 = His bundle response to S_2; H_3 = His bundle response to S_3; H_4 = His bundle response to A_4; S = pacing stimulus; S_1 = basic driven stimulus; S_2 = first extrastimulus; S_3 = second extrastimulus.

TABLE I (Continued)

Propanolol							Procainamide			
RVP* Induction	VEST† Induction	Termination of VT	CL-VT (ms)	Ability to Sustain	RVP* Induction	VEST† Induction	RVP* Induction	VEST† Induction	CL-VT (ms)	Ability to Sustain
(−)	(−)	0	320	+	360–270	280‡	330–290‡	(−)	(−)	(−)
300	300–280	0	320	+	300	310–290	0	(−)	(−)	(−)
330–300	350–300	0	330	+	300–280	260–230	400–280	380–340	380	+
(−)	(−)	+	420	0	(−)	(−)	(−)	(−)	500	0

§ 0 = VT not terminated, not sustained, or not induced; + = VT terminated, sustained, or induced.
¶ (−) = data not generated.
CL-VT = cycle length of VT; RVP = rapid ventricular pacing; VEST = ventricular extrastimulus testing.

noted in 3 patients (cases 1 to 3) and intact ventriculoatrial conduction in 1 (case 4). Both capture and fusion beats were observed with appropriate atrial pacing. The QRS complex was not preceded by a His bundle spike. These findings are consistent with a diagnosis of VT. Sustained VT was inducible with incremental atrial pacing in 1 patient (case 4) (Fig. 3A), double atrial extrastimulus testing in 1 patient (case 2) (Fig. 3B), incremental ventricular pacing in all 4 patients (Fig. 4), and a single or double ventricular extrastimulus in 2 patients (cases 2 and 3). In 2 patients (cases 1 and 4), ventricular extrastimulus induced only 1 or 2 ventricular premature complexes with a QRS morphology similar to that of VT. In the 2 patients with atrial induction of VT, the induction was independent of the development of right BBB or LAD, or both, suggesting that macroreentry involving the bundle branches or fascicles is not likely to be the mechanism of VT (Fig. 3).[10] In 3 patients, the interval between the last ventricular paced beat and the initiating beat of VT or the interval between the ventricular extrastimulus and the initiating beat of VT was inversely related to the ventricular driven cycle length or the coupling interval of the extrastimulus (Fig. 4). In the remaining patient (case 3), no specific relation was found. The cycle length of VT ranged from 320 to 390 ms; alternation of the cycle length was observed in 1 patient (case 1) (Fig. 5A). In all 4 patients VT could be terminated with ventricular premature stimulation or a short burst of rapid ventricular pacing, or both.

Pharmacologic responses (Table I and Fig. 2, 5, and 6): Intravenous verapamil slowed the rate of VT in

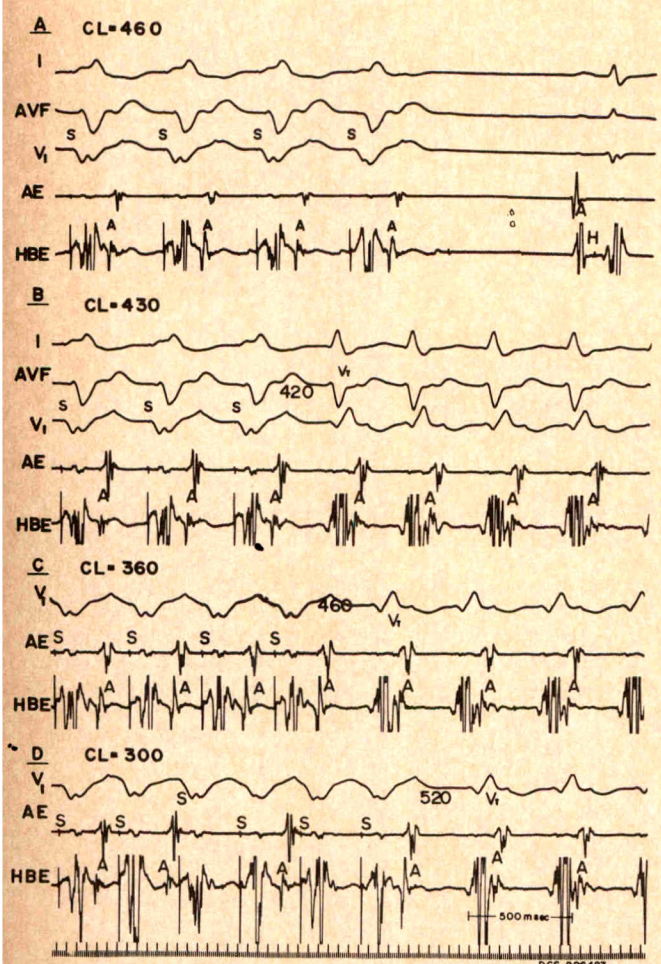

FIGURE 4. Recordings in case 4 showing an inverse relation between the ventricular paced cycle length (CL) and the interval of the last paced beat to the first beat of the VT (S-V_t interval). At a paced cycle length of 460 ms, VT was not induced (**panel A**); at a paced cycle length of 430 ms, VT was induced and S-V_t was 420 ms (**panel B**); at a paced cycle length of 360 ms, VT was induced and S-V_t was 460 ms (**panel C**); at a paced cycle length of 300 ms, VT was induced and S-V_t was 520 ms. V_t = first beat of the induced VT.

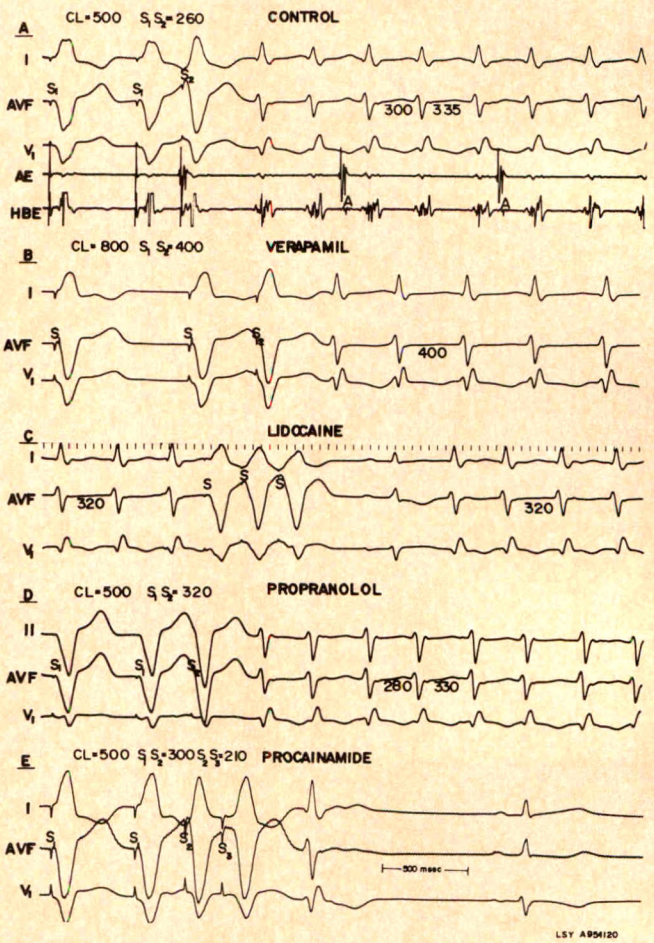

FIGURE 5. Recordings in case 1 showing the effects of verapamil, lidocaine, propranolol, and procainamide on induction of VT. Before drugs, sustained VT was induced during a ventricular paced cycle length of 500 ms at a ventricular coupling interval of 260 ms. Note an alternation of cycle length between 300 and 335 ms occurred during VT (**panel A**). With verapamil, sustained VT was induced during a paced cycle length of 800 ms at a coupling interval of 400 ms. The cycle length of VT lengthened to 400 ms (**panel B**). With lidocaine, the VT could not be terminated with a burst of rapid ventricular pacing which was followed by a sinus captured beat with resumption of the VT at a cycle length of 320 ms (**panel C**). With propranolol, sustained VT was induced during a paced cycle length of 500 ms at a coupling interval of 320 ms. The cycle length of VT again showed an alternation between 280 and 330 ms (**panel D**). With procainamide, only 1 premature ventricular complex with a QRS morphology being similar to that of VT was induced with double premature stimulations coupled to a basic paced cycle length of 500 ms. The first coupling interval was 300 ms and the second 210 ms (**panel E**).

all 4 patients and terminated VT in 3 of them (cases 2, 3, and 4). In 2 of these 3 patients, repeat electrophysiologic study showed an induction of either nonsustained VT (case 2) or 1 to 2 premature ventricular complexes of a QRS morphology identical to that of the VT (case 3) (Fig. 6B). In 1 patient (case 4), neither VT nor premature ventricular complexes were induced, but spontaneous ventricular complexes of a QRS morphology identical to that of the VT was observed after verapamil. The VT of the 1 patient which did not terminate after verapamil (case 1) was terminated with electrical stimulation. Repeat electrophysiologic study in this patient showed an induction of sustained VT (Fig. 5B). Of the 3 patients with induction of either VT or premature ventricular complexes, the induction occurred either at a longer ventricular paced cycle length or at a longer ventricular coupling interval as compared with that in the control study.

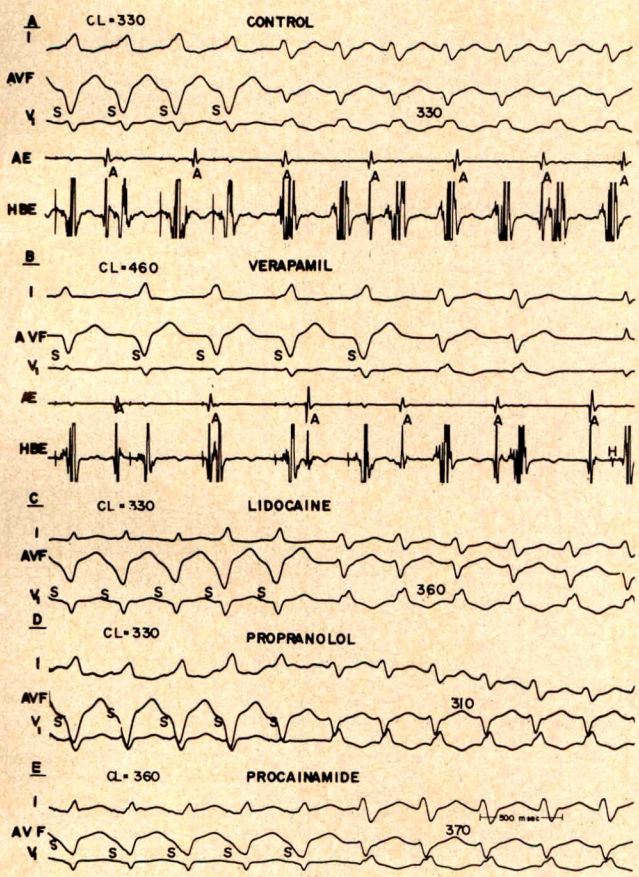

FIGURE 6. Recordings in case 3 showing the effects of verapamil, lidocaine, propranolol, and procainamide on induction of VT. VT was induced with rapid ventricular pacing. Before drugs, sustained tachycardia was induced at a paced cycle length (CL) of 330 ms. The cycle length of VT was 330 ms (**panel A**). With verapamil, 2 premature ventricular complexes with a QRS morphology identical to that of VT were induced at a paced cycle length of 460 ms (**panel B**). With lidocaine, sustained VT was induced at a paced cycle length of 330 ms. The cycle length of VT was 360 ms (**panel C**). With propranolol, sustained VT was induced at a paced cycle length of 330 ms. The cycle length of VT was 310 ms (**panel D**). With procainamide, sustained VT was induced at a paced cycle length of 360 ms. The cycle length of VT was 370 ms **(panel E).**

Intravenous lidocaine did not affect VT in 3 patients. In 1 patient (case 4), lidocaine terminated VT, but nonsustained VT continued to erupt during sinus rhythm. In 2 of the 3 former patients (cases 2 and 3), VT was converted to sinus rhythm with electrical stimulation. In 1 patient (case 1) VT could not be converted to sinus rhythm with electrical stimulation until a bolus of 5 mg of intravenous verapamil was administered (Fig. 5C). Repeat electrophysiologic study in these 3 patients showed induction of sustained VT (Fig. 6C).

Intravenous propranolol did not affect VT in 3 patients, and slowed the rate of VT in 1 patient (case 4). In the latter patient, VT terminated spontaneously, but was followed by repeated eruptions of nonsustained VT. In the former 3 patients, VT was terminated with electrical stimulation and repeat electrophysiologic study showed induction of sustained VT (Fig. 5D and 6D).

With oral procainamide, sustained VT could be induced in 1 patient (case 3) (Fig. 6E); 1 or 2 premature complexes of a QRS morphology identical to that of VT occurred in 1 patient (case 1) (Fig. 5E); and neither VT nor premature ventricular complexes could be induced in 1 patient (case 2). In the remaining patient (case 4), repeated eruptions of nonsustained VT were noted after procainamide administration. The cycle length of VT was longer after procainamide (Fig. 6A and 6E). Of the 2 patients with either induction of VT or premature ventricular complexes after procainamide (cases 1 and 2), induction occurred at either a longer ventricular paced cycle length or at a longer ventricular coupling interval as compared with that of the control study. The serum procainamide concentration was, respectively, 5.5, 6.9, 6.5, and 9.3 μg/ml in the 4 patients.

Discussion

The VT described in this study was unique in that (1) it occurred in young, asymptomatic patients without obvious organic heart disease; (2) the electrocardiogram during sinus rhythm showed a repolarization abnormality over the inferior and lateral precordial leads; (3) the QRS complex during the episodes of VT showed a pattern of right BBB and LAD; (4) the VT was inducible with ventricular stimulation and also with atrial stimulation on occasion; and (5) it responded to verapamil. These findings are similar to those in a recent study by Zipes et al[6] in 3 patients and Belhassen et al[14] in 1. All these patients had no demonstrable organic heart disease and all showed a QRS morphology of right BBB and LAD during VT. Treadmill exercise provoked VT in 1 patient.[6] In this study we further observed that a repolarization abnormality was frequently present in these patients and that VT was responsive to verapamil, partially responsive to procainamide, and nonresponsive to both lidocaine and propranolol. We suggested that VT in this group of patients represents a distinct clinical entity with unique electrocardiographic, electrophysiologic, and electropharmacologic properties.

Although reentry is the mechanism of sustained VT in patients with previous myocardial infarction or with other organic heart disease, the distinction between

reentry and triggered automaticity may not be possible using the catheter stimulatory and recording techniques.[12] Reentrant VT is characterized by (1) induction and termination of VT with appropriate electrical stimulation[1,4,6]; (2) demonstration of an inverse relation between the ventricular paced cycle length and the interval of the last ventricular paced beat to the initiating beat of VT or between the ventricular coupling interval and the interval of the ventricular coupled beat to the initiating beat of VT[1,6,12]; (3) demonstration of delayed conduction with a fragmented electrogram at the site of the reentrant circuit[5]; and (4) the responsiveness to procainamide and quinidine, but rarely to verapamil or propranolol.[13,14] The occurrence of alternation in cycle length during tachycardia is also suggestive of reentry, as it is seen frequently in patients with atrioventricular or atrioventricular nodal reentrant tachycardia.[15] VT due to triggered automaticity can also be initiated and stopped by premature stimulation or rapid pacing.[12] In 1 patient reported on by Zipes et al,[6] the number of induced premature ventricular complexes was related to the coupling interval of the premature beat, to whether 1 or 2 premature beats were introduced, and to the cycle length of the basic driven beats. They suggested that triggered automaticity could be the mechanism in this patient, as the amplitude of the triggered after-depolarization increases with the shortening of the driven cycle length or the coupling interval of the premature stimulation. Nevertheless, we believe that this phenomenon cannot absolutely exclude the possibility of reentry. Sustained reentry depends on a revolution time of longer duration than the effective refractory period of the reentrant circuit. Because the effective refractory period of the His-Purkinje and ventricular system shortens with shortening of the cycle length, induction of sustained VT is likely to occur at a shorter basic driven cycle length or a shorter coupling interval. In addition, a reflex increment of the sympathetic tone at a shorter driven cycle length or coupling interval may result in shortening of the effective refractory period and thus may facilitate induction of sustained tachycardia.

Likewise, the antiarrhythmic responses of VT do not suggest a specific mechanism. Procainamide, quinidine, lidocaine, and propranolol may affect reentrant VT by changing both the effective refractory period and the conduction time of the circuit. They may affect the VT due to triggered automaticity by decreasing the amplitude of the after-depolarization.[16–18] The fact that verapamil exerted a striking effect on the VT in our patients, nevertheless, suggests that slow-response tissue was involved in the genesis of VT.[16–18] Although reentry was likely to be the mechanism of VT in our patients, the possibility of triggered automaticity cannot be excluded absolutely.

A transient repolarization abnormality has been observed in patients with intermittent left BBB, with intermittent ventricular preexcitation, and after termination of both ventricular pacing and ventricular tachycardia.[19,20] The repolarization abnormality in our patients was observed over a prolonged period and thus did not appear to reflect a transient repolarization abnormality secondary to termination of VT.

In conclusion, we have described a distinct entity of recurrent, sustained VT occurring in young, asymptomatic patients without obvious heart disease. In these patients, the electrocardiogram taken during sinus rhythm frequently shows a repolarization abnormality over the inferior and lateral precordial leads. The VT is associated with a QRS morphology of right BBB and LAD and is inducible with atrial or ventricular stimulation, or both. Our study suggests that verapamil is highly effective and procainamide is partially effective, whereas lidocaine and propranolol are generally ineffective in the treatment of this arrhythmia.

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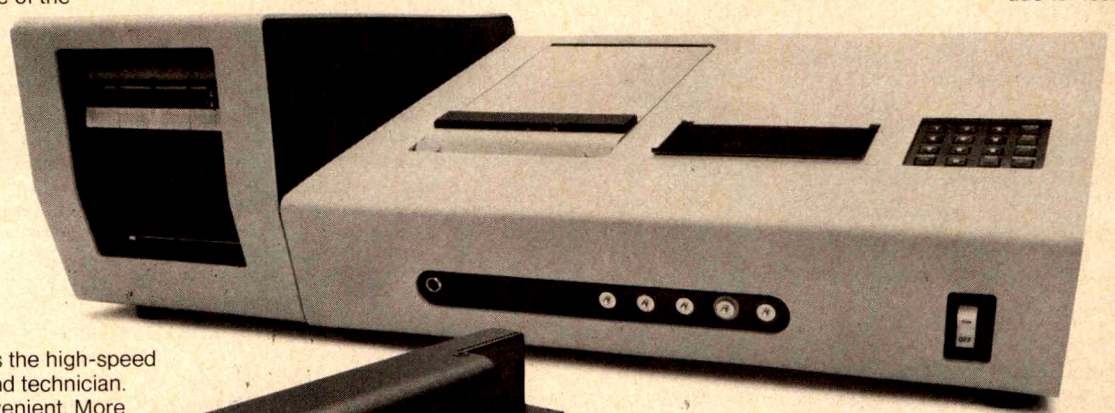

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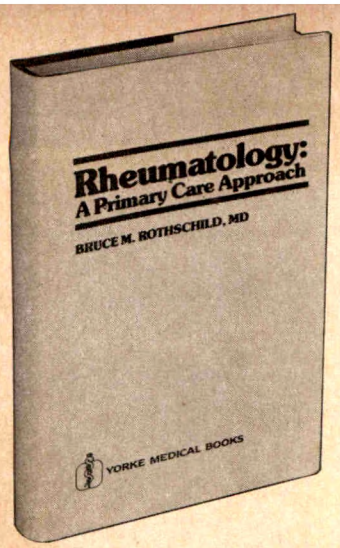

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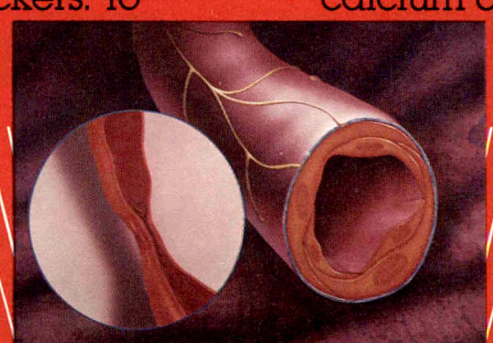

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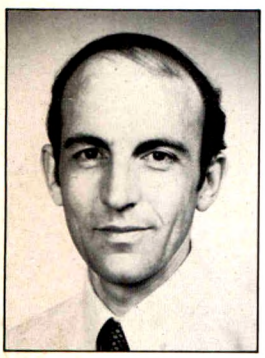

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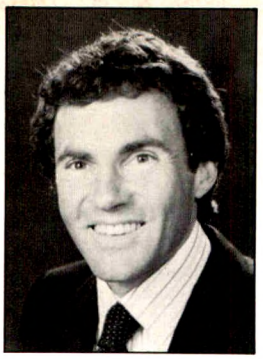

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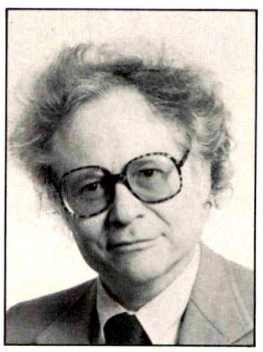

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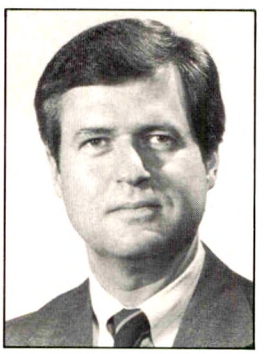

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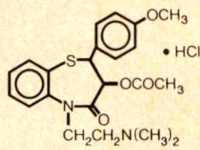
DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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Indications and Contraindications
The medical literature describes currently accepted indications and contraindications for the various pacing/sensing modes. However, the physician's clinical experience and judgment must ultimately determine the pacing mode best suited to the patient's needs.

When spontaneous beats are expected, a sensing mode (inhibited or triggered) is indicated. *Asynchronous pacing is contraindicated for long-term pacing when inherent activity is present or likely to be present in the chamber being paced.*

Pacing of the ventricles (VVI or VVT) is indicated for controlling slow heart rate in patients with A-V block and/or sick sinus syndrome. Atrial pacing (AAI or AAT) is indicated for controlling heart rate, increasing cardiac output, and suppressing premature ventricular contractions (PVCs) in patients with intact A-V conduction and sick sinus syndrome. *Atrial pacing is contraindicated when A-V conduction disturbances are present.*

Atrial-synchronized ventricular pacing (VVD or VAT) and dual-chamber pacing (DVI or DDD) are indicated for patients who would benefit from restoration of atrial contribution to cardiac output and the control of heart rate. Atrial-synchronized ventricular pacing is indicated for patients with permanent heart block and normal atrial rhythm. Dual-chamber pacing is indicated for A-V conduction disturbances with sinus node dysfunction (sinus bradycardia with A-V block, bradytachy syndrome). *Atrial-synchronized ventricular pacing and automatic dual-chamber demand pacing modes are contraindicated in the presence of persistent atrial flutter or atrial fibrillation.* The VVI mode is recommended for these conditions.

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Precautions
Cordis implantable pacers may respond to programmers of other manufacturers. Because of the unknown nature of such response, use only the Cordis Model 255A Programmer III for reprogramming.

Use pacers on a first-in, first-out basis prior to the "Use before" date on the package.

Warnings
None

Adverse Effects
A number of complications related to pacer therapy have been reported in the medical literature. The complications listed below may occur at any time after implantation.

Pacer – battery depletion, electromagnetic interference, component malfunction, decreased sensitivity.

Lead – unsatisfactory electrode position, fracture, displacement, perforation of heart wall, faulty connection with pacer, migration through body tissue.

Patient – reaction, infection/erosion, increase in stimulation threshold, embolism, thrombosis.

Caution: Federal (U.S.A.) law restricts these devices to sale by or on the order of a physician.

Prior to use, refer to the *Instructions for Use* for more information.

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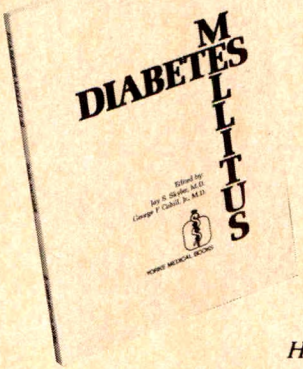

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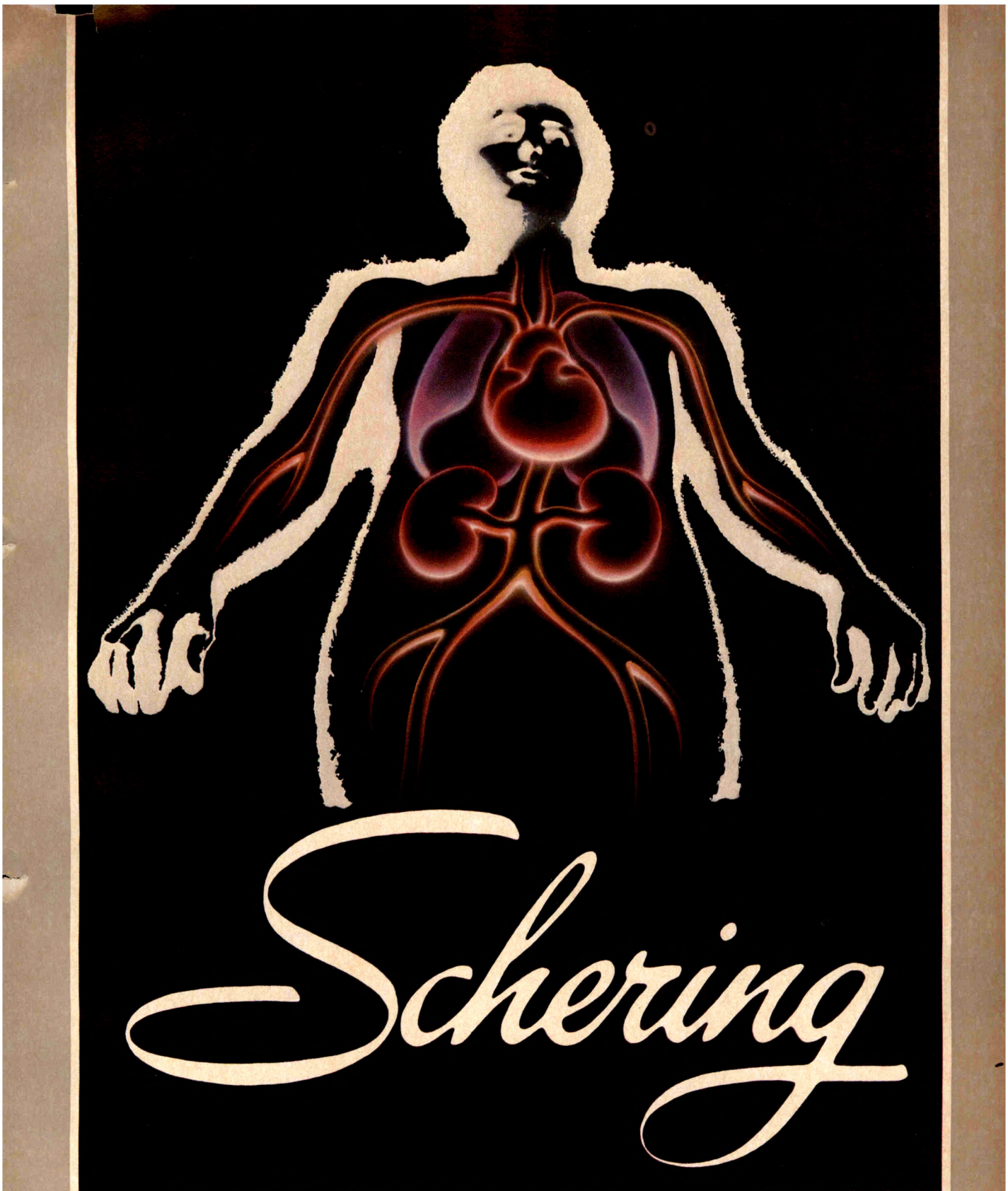

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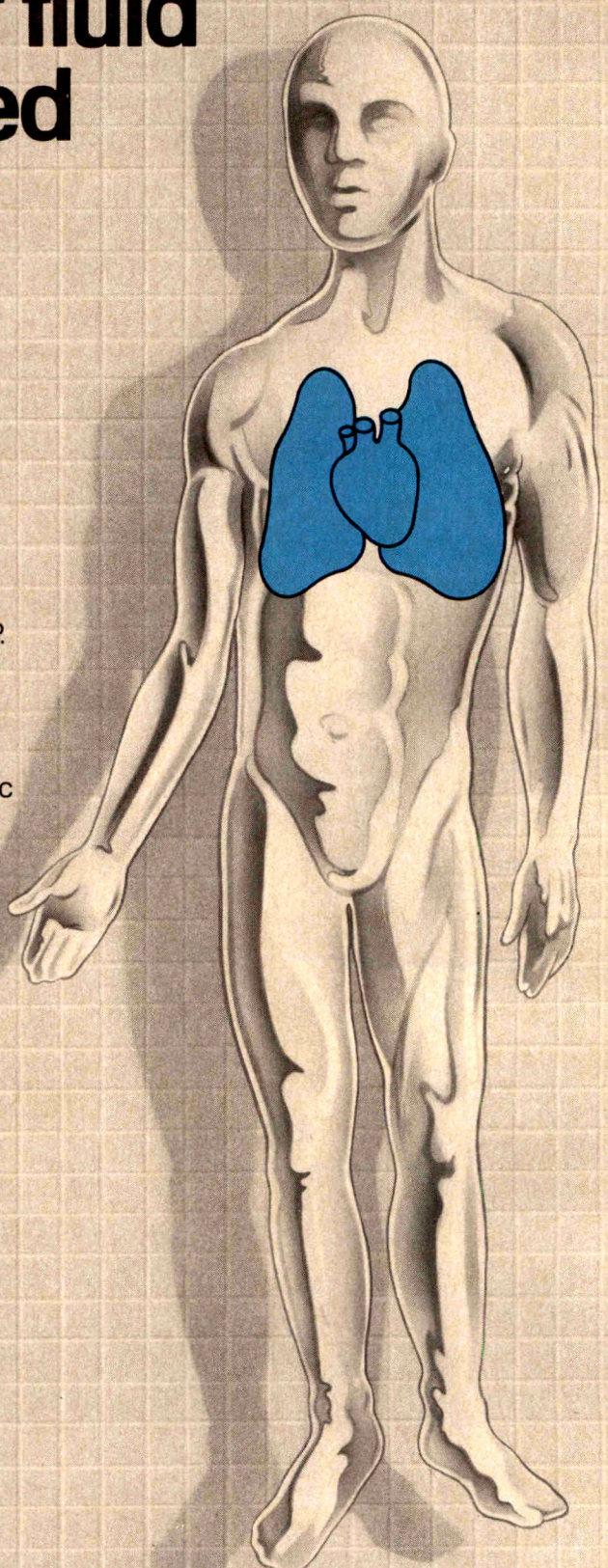
A familiar name in medicine becomes

Therapeutic challenge:

Redistribution of fluid in CHF associated with acute MI



In Early CHF[1]

Pulmonary congestion with increased preload.

Findings: Elevated preload, elevated blood pressure, normal or slightly decreased cardiac output, PCWP greater than or equal to 18 mm Hg.

Therapeutic goal:
Reduce pulmonary congestion, lower PCWP to 15 to 18 mm Hg.

In Late CHF[1]

Pulmonary congestion with increased preload and afterload.

Findings: Low cardiac output, depressed blood pressure, and high PCWP.

Therapeutic goal:
Reduce pulmonary congestion, preload, and afterload, increase cardiac output, and lower PCWP to 15 to 18 mm Hg.

Why wait for the patient to become unresponsive to traditional diuretic/digitalis therapy?

1. Forrester JS, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;295:1356-1362, 1404-1413.

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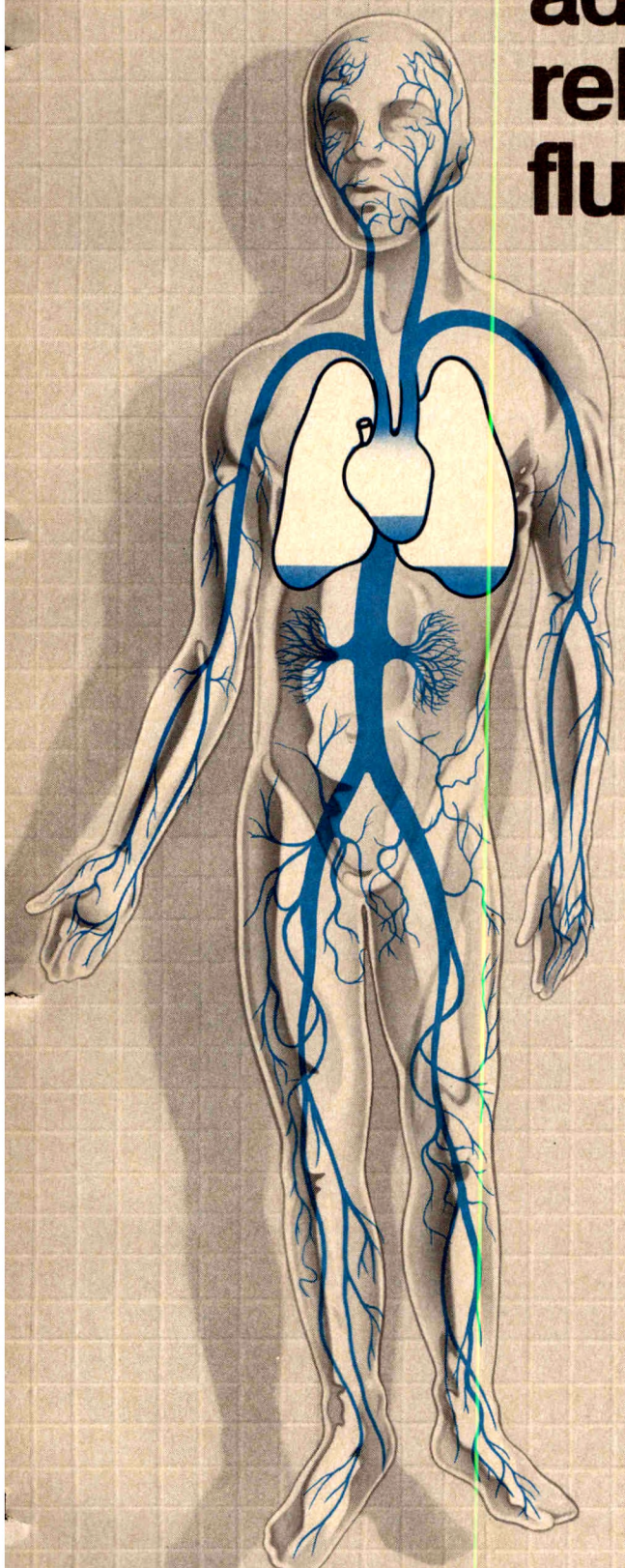
Give Tridil® (nitroglycerin) adjunctively to help relieve the fluid-burdened heart



In a dose-related manner, Tridil produces dilation of both arterial and venous beds—for a therapeutic redistribution of fluid.

Suggested therapy in early CHF

If blood pressure is normal:
Tridil to reduce preload and PCWP. Diuretics to decrease fluid volume.

If blood pressure is elevated:
Tridil should be initiated immediately to decrease preload, PCWP, and blood pressure, while maintaining coronary perfusion.

Suggested therapy in late CHF

If blood pressure is normal or only moderately depressed:
Vasopressors and Tridil adjunctively, with continuous hemodynamic monitoring.

If blood pressure is significantly depressed:
Vasopressors and Tridil adjunctively to reduce preload, afterload, and PCWP. Dopamine to increase the contractility of the myocardium. PCWP should be monitored.

Use of nonabsorbing Tridilset®

Sorptive loss of Tridil may range up to 80% when infused through a conventional PVC administration set[2] To overcome this problem, administer Tridil through Tridilset administration set or Tridilset V.I.P.™ volumetric pump connector set.

The most frequent adverse reaction in patients treated with Tridil is headache. Please see the following page for a brief summary of prescribing information. Note: Tridil is a potent drug and must be diluted before infusion.

For additional information, contact the Medical Services Department, American Critical Care, division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

2. Baaske DM, et al: Administration set suitable for use with intravenous nitroglycerin. *Am J Hosp Pharm* 1982;39:121-122.

TRIDIL® (nitroglycerin) SYSTEM

American Critical Care

TRIDIL® (nitroglycerin)

Brief Summary of Full Prescribing Information

NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

CAUTION

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

CONTRAINDICATIONS

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinyl chloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,® an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION

(For complete information, please see Full Prescribing Information)

NOT FOR DIRECT INTRAVENOUS INJECTION

TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

HOW SUPPLIED

NDC 0094-0090-05, 25 mg-5 ml ampul. NDC 0094-0090-10, 50 mg-10 ml ampul. Each ml contains 5 mg nitroglycerin. Protect from freezing.

December 1981

Distributed by

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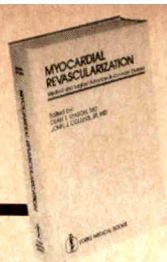
A114



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Platelet Alpha$_2$ Adrenoreceptors in Chronic Congestive Heart Failure

ROBERT J. WEISS, MD, MICHAEL TOBES, PhD, CURTIS E. WERTZ, BA, and CHARLES B. SMITH, MD, PhD

Patients with chronic congestive heart failure (CHF) are known to have elevated plasma concentrations of norepinephrine. Although this elevation of catecholamines in plasma may facilitate myocardial contractility, it may also be toxic to the myocardium in the long term. The alpha$_2$ adrenoreceptor located on noradrenergic nerve terminals regulates neuronal norepinephrine release by feedback inhibition. This receptor is also located on human blood platelets. This study determines the status of platelet alpha$_2$ adrenoreceptors in 16 patients with CHF (class I and II in 7 and class III and IV in 9) and in 26 normal volunteers. Specific high-affinity binding of the alpha$_2$ agonist ^{3}H-clonidine and the alpha$_2$ antagonist ^{3}H-yohimbine was used to determine the number (B_{max}) of alpha$_2$ receptors and the dissociation constant (K_D) for the 2 ligands. In the control population, the B_{max} (in fmol/mg protein) for ^{3}H-clonidine was 33 ± 2 and for ^{3}H-yohimbine was 165 ± 12. There was a 25% difference in the maximum number of specific binding sites for ^{3}H-clonidine in the class III/IV group (B_{max} 24 ± 2, $p < 0.05$) and a 43% difference in the maximum number of specific binding sites for ^{3}H-yohimbine (B_{max} 94 ± 9; $p < 0.005$). There was a smaller but nonsignificant difference in the number of receptors on platelets from patients in the class I and II group. The K_D's were similar in all 3 groups. These differences correlated well with the increases in plasma norepinephrine levels between the normal group (273.8 ± 44.1 pg/ml) and the class III/IV group (1333.5 ± 244.9, $p < 0.0005$). This study supports the hypothesis that increased levels of circulating norepinephrine in CHF lead to a decrease in platelet alpha$_2$ adrenoreceptors. Further studies should be performed to determine whether pharmacologic stimulation of these receptors might lead to a decrease in the neuronal release of that norepinephrine which might be toxic to the myocardium. Monitoring of platelet alpha$_2$ adrenoreceptor number may provide a guide to therapy of CHF.

Patients with chronic congestive heart failure (CHF) are known to have elevated concentrations of circulating norepinephrine. The degree of elevation is related to the degree of left ventricular dysfunction.[1–3] Although the circulating norepinephrine may increase myocardial contractility, persistently elevated levels have been shown to be toxic to the myocardium in experimental animals[4–6] and in humans.[7,8]

The alpha$_2$ adrenoreceptor is located presynaptically on noradrenergic nerve terminals and has been shown to exert a negative feedback inhibition upon norepinephrine release when stimulated.[9–11] If neurogenically released norepinephrine has a detrimental effect on the myocardium, alterations in alpha$_2$ adrenoreceptor function might be of potential importance in CHF. Human blood platelets have been suggested as a model for the indirect study of changes in nerve cell function.[12] Studies which use receptor binding techniques and which measure the relative order of potencies of various adrenergic agonists and antagonists in displacing bound radioligand have shown that human platelets have alpha$_2$ adrenoreceptors similar to those present on noradrenergic nerve terminals.[13,14] Changes in the number and affinity of alpha$_2$ adrenoreceptor binding sites in the rat brain after various interventions have been well correlated with similar changes on human blood platelets.[14–17] These have also been correlated with changes in norepinephrine release and tension developed in field stimulation experiments upon isolated rat atrial strips.[18]

From the Departments of Pharmacology and Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. This study was supported in part by Grant MH-36226 from the U.S. Public Health Service, Bethesda, Maryland, and a grant from the Michigan Heart Association, Lathrup Village, Michigan. Manuscript received January 17, 1983; revised manuscript received March 21, 1983, accepted March 25, 1983.

Address for reprints: Charles B. Smith, MD, PhD, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan 48109.

The hypothesis of the present study was that alpha$_2$ adrenoreceptors on human blood platelets would be decreased by the increased circulating levels of norepinephrine found in severe chronic CHF and as such mirror changes found in the presynaptic site.

Methods

Patient population: Blood was obtained by venipuncture from healthy male and female volunteers (mean age 40 ± 3 years, n = 26). These control subjects were compared with patients with chronic CHF who were selected and classified by history, physical examination, and invasive hemodynamic monitoring findings. The patients were divided into standard New York Heart Association[19] class I and II (Group 1: mean age 62 ± 2 years, n = 7) and class III and IV groups (Group 2: mean age 68 ± 4 years, n = 9). The cause of the CHF was valvular (Group 1 = 3, Group 2 = 2), ischemic (Group 1 = 3, Group 2 = 5), and idiopathic (Group 1 = 1, Group 2 = 2). The 2 groups did not differ in the distribution of causes. Previous work[16] has shown the lack of age or sex dependency of either the total number or the affinity of platelet alpha$_2$ adrenoreceptors. None of the patients were taking alpha-adrenergic agonists or antagonists, indirectly acting adrenergic drugs, or inhibitors of norepinephrine uptake for at least 1 month before the study.

Written informed consent was obtained from all patients. This study was approved by the University of Michigan's Institutional Review Board. All assays were done without the knowledge of the patient's clinical characteristics.

Isolation of platelet membranes and radioligand binding assay: Platelet membranes were obtained by the method described by Garcia-Sevilla et al.[14] Briefly, 50 ml of blood was collected in polyethylene tubes which contained acid-citrate dextrose (ACD, 8:1, volume/volume). The blood was centrifuged at 160 *g* for 10 minutes (25°C), and the platelet-rich plasma was titrated to pH 6.5 with the ACD solution. This was then recentrifuged at 5,100 *g* for 15 minutes (25°C) to obtain a platelet pellet. The pellet was washed twice with 5 ml of Tyrode's buffer (m*M* concentrations: sodium chloride 137, potassium chloride 2.7, sodium biphosphate 0.36, magnesium chloride 0.10, sodium bicarbonate 12.0, dextrose 0.56, pH 8.0) and recentrifuged for 15 minutes at 5,100 *g*. The pellet was lysed by homogenization in 2 ml of ice-cold hypotonic buffer (Tris-EDTA, 5 m*M*, pH 7.5). The platelet membranes were obtained by centrifugation at 39,000 *g* for 10 minutes and then resuspended in the Tris incubation buffer (m*M*: Tris-hydrochloric acid 50, magnesium chloride 10, pH 7.5) used in the binding assay.

Total binding of ^{3}H-clonidine, an alpha$_2$-adrenoreceptor agonist, and of ^{3}H-yohimbine, an alpha$_2$-adrenoreceptor antagonist (New England Nuclear, Boston, Massachusetts) was measured in 1 ml aliquots of the fresh platelet membranes (0.254 ± 0.054 mg protein) which were incubated in duplicate at 25°C for 20 minutes with the radioligand. Nonspecific binding was determined by adding unlabelled clonidine or yohimbine (10^{-5} *M*), in addition to the respective tritiated ligand, to a second pair of incubates. Specific binding was

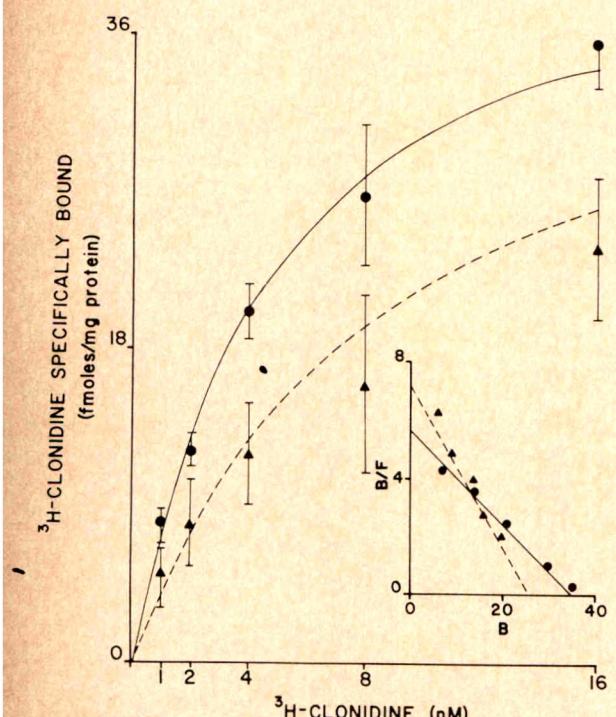

FIGURE 1. Specific binding of ^{3}H-clonidine to platelet membranes from normal subjects (**solid line**) and from patients with class III and IV congestive heart failure (**dashed line**) as a function of increasing concentrations (1 to 64 n*M*) of the ligand. **Ordinate,** ^{3}H-clonidine specifically bound (fmol/mg protein). **Abscissa,** concentration of ^{3}H-clonidine (n*M*). **Inset,** Scatchard plot showing the change in number of the high affinity binding site (normal subjects: B_{max} = 33 ± 2 fmol/mg protein, K_D = 5.5 ± 0.6 n*M* versus class III and IV: B_{max} = 24 ± 2, K_D = 3.4 ± 0.6 n*M*; $p < 0.05$). Results are expressed as the mean ± standard error of the mean. B = specifically bound ligand; B/F = specifically bound ligand/free ligand.

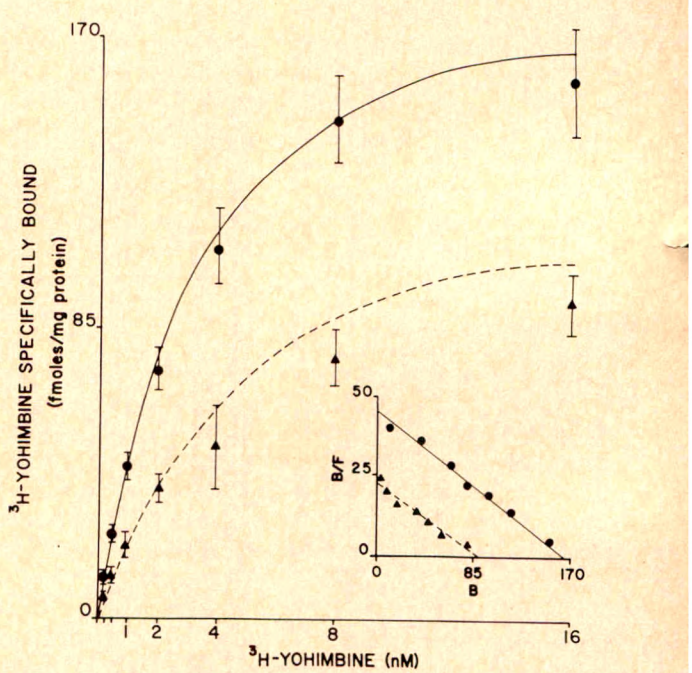

FIGURE 2. Specific binding of ^{3}H-yohimbine to platelet membranes from normal subjects (**solid line**) and from patients with class III and IV congestive heart failure (**dashed line**) as a function of increasing concentrations (0.25 to 16 n*M*) of the ligand. **Ordinate,** ^{3}H-yohimbine specifically bound (fmol/mg protein). **Abscissa,** concentration of ^{3}H-yohimbine (n*M*). **Inset,** Scatchard plot showing the change in number of the single binding site (normal subjects: B_{max} = 165 ± 12 fmol/mg protein, K_D = 4.0 ± 0.5 n*M* versus class III and IV: B_{max} = 94 ± 9, K_D = 4.4 ± 0.4; $p < 0.005$). Results are expressed as the mean ± standard error of the mean. B = specifically bound ligand; B/F = specifically bound ligand/free ligand.

defined as the difference between total and nonspecific binding. Incubations were terminated by adding 5 ml of the Tris incubation buffer to the sample. The membrane-bound tritiated ligand was recovered by rapid filtration of the diluted sample under vacuum through Whatman GF/C glass fiber filters. The filters were washed with two 10 ml aliquots of Tris incubation buffer (25°C). The filters were air dried and counted for radioactivity as described by Smith et al.[20] Proteins were determined by the method of Lowry et al.[21]

Catecholamine determination: Catecholamine determinations were performed by the radioenzymatic assay of Passon and Peuler.[22] The rat liver catechol-O-methyltransferase (COMT) was prepared according to the method of Axelrod and Tomchick.[23] All blood samples were collected as described above with the patient recumbent for at least 30 minutes. The samples were immediately centrifuged and the serum was frozen at −70°C.

Statistical analysis: Student's *t* test was used to test for the significance of differences. The level of significance was $p < 0.05$. Correlation coefficients for the binding isotherms were obtained by linear regression analysis which uses the method of least squares.

Results

Binding data: The specific binding of both ^{3}H-clonidine and ^{3}H-yohimbine to platelet membranes from both normal subjects and patients with chronic CHF was both saturable and of high affinity (Fig. 1 and 2). Scatchard analysis of the saturation isotherms again confirmed previous observations[15] that there was no correlation between age or sex and the total number of binding sites (B_{max}) or the affinity (K_D) of the radioligand for the site. The individual data for the control population for ^{3}H-clonidine (n = 26) was $B_{max} = 33 \pm 2$ and $K_D = 5.5 \pm 0.6$, and for ^{3}H-yohimbine (n = 16) was $B_{max} = 165 \pm 12$, and $K_D = 4.0 \pm 0.5$. There was no difference in the means for either ligand when the over 60-year-old subgroup was compared with the under 60-year-old group.

Patients with the more severe CHF, class III and IV (n = 9, Table I) had a 25% decrease in the maximum number of ^{3}H-clonidine binding sites compared with control subjects ($B_{max} = 24 \pm 2$, $p < 0.05$, Fig. 1) with no change in affinity ($K_D = 3.4 \pm 0.6$, difference not significant). There was also a marked decrease in the B_{max} for ^{3}H-yohimbine (43%, $B_{max} = 94 \pm 9$, $p < 0.005$) but no change in the affinity of the ligand for the receptor ($K_D = 4.4 \pm 0.4$, Fig. 2). Patients with class I and II chronic CHF (n = 7, Table II) had binding data with ^{3}H-yohimbine that suggested a trend towards a decrease in B_{max} as compared with normal subjects ($B_{max} = 133 \pm 16$). This was not statistically significant. In this group, there were not enough studies done with ^{3}H-clonidine to analyze.

Plasma catecholamines: Plasma norepinephrine, epinephrine, and dopamine levels were measured in all control subjects and patients. In normal subjects, the norepinephrine value was 273.8 ± 44.1 pg/ml (range 54 to 503). There was a statistically significant increase in norepinephrine levels in patients with class I and II CHF (628.7 ± 97.6 pg/ml, range 338 to 1079; $p < 0.005$) with a far more significant increase in patients with class III and IV CHF (1333.5 ± 244.9 pg/ml, range 642 to 3142; $p < 0.0005$).

There was no significant difference in plasma epinephrine concentration between normal subjects and class I and II patients (normals 57.0 ± 17.4 pg/ml, class I and II 95.0 ± 48.7). Plasma epinephrine level was elevated significantly in patients with class III and IV CHF (117.1 ± 32.0, $p < 0.05$). Although there was no significant difference in plasma dopamine concentration between the normal group (12.5 ± 9.9 pg/ml) and the class I and II CHF group (38.5 ± 19.6), there also was a statistically significant increase in the class III and IV group (94.1 ± 31.1, $p < 0.01$).

There was a striking relationship for each group between an elevated level of plasma norepinephrine and a decrease in the total number of binding sites for the tritiated ligand (Fig. 3).

Discussion

The ^{3}H-clonidine binding site on human platelets has been characterized as an alpha$_2$-adrenoreceptor site similar to that located presynaptically.[13,14] Stimulation of alpha$_2$ presynaptic receptors[24,25] inhibits neurotransmitter release during nerve stimulation, whereas inhibition of the site increases the overflow of norepinephrine after nerve stimulation.

TABLE I ^{3}H-Clonidine and ^{3}H-Yohimbine Binding to Platelet Membranes of Patients With Congestive Heart Failure (Class III and IV)

Patient	Age (yr) & Sex	Plasma Norepinephrine (pg/ml)	^{3}H-Yohimbine Binding K_D (n*M*)	^{3}H-Yohimbine Binding B_{max} (fmol/mg protein)	^{3}H-Clonidine Binding K_D (n*M*)	^{3}H-Clonidine Binding B_{max} (fmol/mg protein)
K14	76M	1,133	4.6	108	. . .	. . .
K19	70F	1,122	3.6	98	. . .	. . .
K21	60M	3,143	2.5	41	. . .	. . .
C1	85M	643	4.0	120	. . .	. . .
C22	57M	813	6.1	62	1.8	17
C23	76F	1,397	4.2	109	2.4	28
C28	64M	1,329	6.3	93	3.2	26
C31	76M	913	4.1	106	4.3	26
C34	40F	1,510	3.9	108	5.3	24
Mean ±SEM	68.1 ±3.8	1,334 ±245	4.4 ±0.5	94 ±9	3.4 ±0.6	24 ±2

B_{max} = maximum number of binding site (fmol/mg protein); K_D = dissociation constant (n*M*); SEM = standard error of the mean.

TABLE II ^{3}H-Clonidine and ^{3}H-Yohimbine Binding to Platelet Membranes of Patients With Congestive Heart Failure (Class I and II)

Patient	Age (yr) & Sex	Plasma Norepinephrine (pg/ml)	^{3}H-Yohimbine Binding		^{3}H-Clonidine Binding	
			K_D (n*M*)	B_{max} (fmol/mg protein)	K_D (n*M*)	B_{max} (fmol/mg protein)
K12	70F	845	5.6	144	...	...
K13	59F	1,079	6.0	157	...	...
K18	56M	626	3.2	111	...	...
K20	59F	604	2.5	192	...	...
C2	72F	499	3.0	109	...	...
C3	62M	338	6.2	113	...	...
C32	65M	409	3.2	84	2.8	24.0
Mean ±SEM	61.8 ±2.0	629 ±98	4.2 ±0.6	133 ±16	...	...

B_{max} = maximum number of binding site (fmol/mg of protein); K_D = dissociation constant (n*M*); SEM = standard error of the mean.

Although a recent review[26] suggested that the number of alpha$_2$ adrenoreceptors on human platelets as determined by ^{3}H-yohimbine binding is not subject to down-regulation, data presented here suggest this is not the case. The total number of binding sites, B_{max}, as defined by ^{3}H-yohimbine binding, was 43% less in the class III and IV CHF patients and 19% less in the class I and II patients as compared with normal subjects. This was statistically significant for the class III and IV patients ($p < 0.0005$). Changes of a similar magnitude were also noted using ^{3}H-clonidine as the radioligand (class III and IV 25%, $p < 0.05$). Other work from our laboratory[14] has shown significant increases in the number of platelet alpha$_2$ adrenoreceptors in other settings, such as a group of depressed patients versus a normal control population. Treatment with tricyclic antidepressants[14] or with electroconvulsive shock therapy[16] led to a significant decrease in the number of these binding sites. These changes are mirrored by changes in the presynaptic alpha$_2$ adrenoreceptor in the rat brain after identical interventions.[17] It has been suggested that changes in receptor number may not be of physiologic importance.[26] Again, work in our laboratory has correlated decreases in alpha$_2$-adrenoreceptor number in rat brain after long-term tricyclic antidepressant drug treatment[18] with increased norepinephrine release from adrenergic neurons in the isolated rat left atrium.[18]

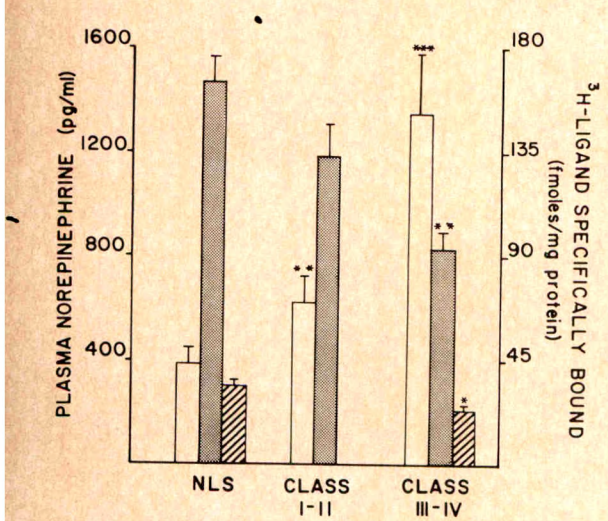

FIGURE 3. Relationship of plasma norepinephrine levels (**open bars**) and the maximum number of ^{3}H-yohimbine (**shaded bars**) and ^{3}H-clonidine (**cross-hatched bars**) binding sites. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0005$ (between control group and group with class III/IV failure). NLS = normal subjects.

Further evidence of the physiologic importance of this decrease in the number of presynaptic receptors in patients with severe congestive failure may be found in the recent work by Swedberg et al.[27] They defined a correlation between myocardial norepinephrine release and the stroke work index. As left ventricular function decreased, there was an increase in norepinephrine released, as measured by the arterial-coronary sinus difference. In our study, a decrease in left ventricular function was associated with fewer alpha$_2$ adrenoreceptors, a condition which would permit increased neuronal norepinephrine release.

Older work by Covell et al,[28] however, was interpreted as not suggesting increased neuronal release of norepinephrine in CHF. They showed that stimulation of the right cardio-accelerans nerve in the dog produced sharply diminished increases in heart rate and right ventricular contractile force in animals with right heart failure versus normal control animals. In addition, they showed that the myocardial response to exogenous norepinephrine was unchanged from normal values, which suggested to them that the quantity of neurotransmitter released per nerve impulse was reduced in their experimental model of heart failure. That the cardiac norepinephrine depletion found in chronic CHF did not affect the contractile function of cardiac muscle was shown with cat papillary muscle isolated from chronically denervated heart[29] and with isolated rat hearts.[30] One would have, perhaps, expected increased release of norepinephrine with the decrease in number of platelet alpha$_2$ adrenoreceptors. This inconsistency may possibly be explained by a decrease in cardiac stores of norepinephrine in CHF,[31–33] a defect in binding or synthesis of catecholamines in congestive failure,[34] or by a decrease in tyrosine hydroxylase activity.[35] Although it is believed that the platelet alpha$_2$ adrenoreceptor "down-regulates" in response to the high plasma concentrations of norepinephrine, it is possible that any similar change in the neuronal receptors in the

myocardium may occur in order to permit an increase in norepinephrine release. The increased release of catecholamine would permit increased inotropic support of the failing myocardium. That different tissues may respond differently in CHF has been suggested by data which showed decreased myocardial norepinephrine stores in light of normal renal stores.[32]

In our study, there was a significant increase in plasma norepinephrine levels in patients with class III and IV CHF versus those of normal volunteers ($p < 0.0005$) and also in those with only class I or II CHF ($p < 0.005$). Although the blood samples were obtained by venipuncture and not through an indwelling catheter, previous work suggests this does not affect the plasma norepinephrine concentration.[36] These values are consistent with previously reported studies[1,4,5] which correlated an elevated plasma norepinephrine level with the degree of left ventricular dysfunction. There were no significant differences in the levels of epinephrine and dopamine in the normal subjects and the class I/II group, although there was a difference in the levels of epinephrine ($p < 0.05$) and dopamine ($p < 0.01$) in the normal groups and the class III/IV group.

This study suggests that in CHF, human platelet $alpha_2$ adrenoreceptors may serve as a marker of elevated levels of circulating norepinephrine. Changes in the platelet receptor number may be a method of monitoring the therapy of congestive failure. Identification and characterization of these receptors suggest the possibility of using $alpha_2$-agonist agents such as clonidine or alpha methyldopa to stimulate these inhibitory sites and thus decrease norepinephrine release. This may, in turn, protect the myocardium from the excessively high levels of circulating norepinephrine as has been done with beta-adrenergic blockade. Further studies in humans are needed to ascertain whether successful therapy in patients with CHF restores the receptor number to normal. These changes should be correlated in animal models of heart failure with neuronal release of norepinephrine after nerve stimulation. Such changes may prove important in developing new therapeutic strategies in the treatment of CHF.

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Cardiovascular Effects of Breathing 95 Percent Oxygen In Children With Congenital Heart Disease

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The hemodynamic effects of breathing 95% oxygen were evaluated in 26 children with congenital heart disease. Aortic, pulmonary arterial, right atrial, and pulmonary arterial wedge pressure, aortic and pulmonary artery oxygen saturation, and blood gas, cardiac index, and heart rate were measured in room air and after each patient had breathed 95% oxygen for 10 (n = 26) and 20 (n = 5) minutes. Measurements were repeated with the patient again breathing room air for 10 (n = 11) and 20 (n = 6) minutes. After 10 minutes of 95% oxygen, arterial partial pressure of oxygen increased from 85 ± 13 to 420 ± 89 torr ($p < 0.001$). Aortic mean pressure increased from 80 ± 10 to 83 ± 10 mm Hg ($p < 0.01$), and systemic vascular resistance increased from 20 ± 7 to 26 ± 8 U ($p < 0.001$). The cardiac index decreased by 21% from 3.96 ± 0.94 to 3.12 ± 0.74 liters/min/m^2 ($p < 0.001$) and the stroke index decreased by 11% ($p < 0.001$). A 23% decrease in oxygen consumption ($p < 0.001$) was observed, and oxygen transport decreased from 763 ± 179 to 600 ± 161 ml O_2/min/m^2 ($p < 0.001$). Cardiac index, stroke index, and systemic vascular resistance did not return to normal until 20 minutes after cessation of oxygen breathing. To determine whether reflex bradycardia is responsible for these oxygen-induced hemodynamic changes, heart rate was kept constant by atrial pacing in a second group of 5 patients. In these children, significant decreases in cardiac index, stroke index, and oxygen consumption, and increases in systemic vascular resistance also occurred with 95% oxygen. Thus, in children with acyanotic congenital heart disease, hyperoxia increases aortic pressure and systemic vascular resistance and decreases cardiac index, stroke index, oxygen consumption, and oxygen transport.

The medical and surgical therapy of children with heart disease frequently includes administration of oxygen. The goal is to improve systemic oxygen delivery in patients with cyanosis, heart failure, or pulmonary edema. Previous studies have indicated, however, that oxygen itself may significantly alter cardiovascular hemodynamic function. In animals and in adults without heart disease, high inspired oxygen concentrations have been shown to increase systemic arterial pressure and systemic vascular resistance (SVR), and to decrease heart rate and cardiac index (CI).[1–6] Similar studies have not been performed in children or in patients with heart disease. The present study was therefore designed to evaluate the hemodynamic effects of oxygen administration in children with acyanotic congenital heart disease.

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Methods

The study involved 31 children with congenital heart disease who were undergoing diagnostic cardiac catheterization. There were 18 males and 13 females ranging in age from 0.2 to 15.5 years (mean 5.5). Twenty patients had previously undergone surgical repair of the following congenital heart defects: ventricular septal defect (n = 10), endocardial cushion defect (n = 3), patent ductus arteriosus (n = 3), D-transposition (n = 2), tetralogy of Fallot (n = 1), and total anomalous pulmonary venous return (n = 1). The remaining patients, who not been operated on, had aortic stenosis (n = 3), cardiomyopathy (n = 3), aortic regurgitation (n = 1), mitral regurgitation (n = 1), pulmonary stenosis (n = 1), L-transposition with pulmonary stenosis (n = 1), and primary pulmonary hypertension (n = 1). No patient had an intracardiac shunt documented at cardiac catheterization although several appeared to have a small intrapulmonary right-to-left shunt. Five patients (Table I: Patients 2, 12, 14, 20, 25) had congestive heart failure requiring treatment with digoxin and diuretics. Patients 2, 24, 25 and 26 had moderate to severe pulmonary artery hypertension (mean pulmonary pressure ≥0.5 mean aortic pressure). Patients 1, 2, 5 to 7, 26 and 31 had multiple episodes of pneumonia and evidence on chest roentgenography of chronic pulmonary disease.

TABLE I Hemodynamic Effects of 95% Oxygen in 26 Children With Congenital Heart Disease: Baseline Data in 21% Oxygen and Data in 95% Oxygen for 10 Minutes

			21% Oxygen (Baseline)								95% Oxygen (10 Minutes)							
Patient	Diagnosis	Age (yr)/BSA	HR	CI	SI	AoP	SVR	VO_2	PaO_2	$PaCO_2$	HR	CI	SI	AoP	SVR	VO_2	PaO_2	$PaCO_2$
1	PDA ligation	6.5/0.70	79	4.57	58	72	14	125	70	41	72	3.14	44	78	23	86	482	43
2	Primary pulmonary hypertension	6.2/0.89	124	1.91	15	91	47	159	55	35	125	1.79	14	98	51	126	382	38
3	VSD repair	6.8/0.78	107	5.00	47	75	14	186	97	37	113	4.48	40	80	17	129	460	40
4	PDA ligation	10.5/1.10	68	3.09	45	82	23	126	98	40	58	2.36	41	82	30	94	442	42
5	VSD repair	3.2/0.48	120	4.79	40	83	16	173	82	51	105	4.48	43	84	18	...	399	50
6	VSD repair	2.1/0.43	120	4.27	36	62	13	132	85	44	112	3.67	33	70	17	108	466	44
7	ECD repair	2.0/0.51	110	4.15	38	77	18	139	83	44	100	3.17	32	73	22	...	368	45
8	VSD repair	6.2/0.71	105	5.40	51	90	16	196	92	39	85	3.66	43	100	26	162	488	30
9	VSD repair	1.0/0.36	80	3.61	45	70	18	188	84	37	70	2.77	40	75	25	149	342	43
10	AS	8.5/0.90	78	4.11	53	88	20	119	86	43	67	3.22	48	90	26	116	448	41
11	ECD repair	3.1/0.58	96	4.17	43	80	18	134	84	39	74	3.44	46	80	22	109	348	44
12	MR	11.8/1.00	86	3.30	38	80	22	117	99	43	79	2.46	31	80	30	96	450	37
13	AS	6.1/0.72	104	3.82	37	103	26	100	88	36	75	2.94	39	101	32	93	510	36
14	Cardiomyopathy	2.1/0.46	96	4.39	46	70	15	145	100	36	94	3.58	38	72	19	123	480	39
15	TAPVR repair	12.2/1.08	67	3.64	54	75	19	123	77	39	64	3.24	51	80	23	129	448	35
16	D-TGA, Mustard	1.6/0.47	115	3.19	28	78	23	118	73	36	108	2.72	25	85	29	98	260	49
17	ECD repair	5.0/0.57	107	3.75	35	72	17	147	83	46	102	3.30	32	80	22	134	392	38
18	AS	15.5/1.90	85	4.53	53	90	18	175	93	40	96	4.10	43	95	22	92	459	33
19	PS	1.4/0.40	116	3.92	34	90	22	113	81	39	96	3.35	35	90	25	80	495	34
20	AR	0.2/0.21	114	2.76	24	70	24	70	100	40	115	2.52	22	72	26	85	486	35
21	VSD repair	2.0/0.53	85	4.39	52	70	15	143	100	37	77	3.15	41	77	22	96	240	42
22	L-TGA, PS	12.0/1.25	135	3.91	29	85	21	123	80	37	140	3.21	23	88	26	87	489	37
23	Cardiomyopathy	0.3/0.20	141	6.25	44	103	16	242	80	40	126	4.16	33	103	24	147	510	40
24	VSD repair	3.5/0.81	88	2.96	34	70	21	108	82	39	73	2.44	33	68	25	78	515	39
25	Cardiomyopathy	3.0/0.46	143	2.39	17	85	31	182	56	40	126	1.54	12	77	43	99	401	36
26	PDA ligation	7.8/0.63	111	4.60	41	69	14	171	63	53	101	3.96	39	78	18	76	169	62
	Mean		103	3.96	39.8	80	20.1	144	84	40	94.3	3.12	35.3	82.9	26	112	420	40
	±SD		±21	±0.94	±11.1	±10	±6.9	±37	±13	±4	±22.4	±0.74	±9.7	±9.9	±7.7	±23	±89	±6
	Significance*		...	...	...	...	...	...	...	...	†	†	†	‡	†	†	†	...

* Compared with baseline value in 21% oxygen.
† $p < 0.001$.
‡ $p < 0.01$.

AoP = mean aortic pressure (mm Hg); AR = aortic regurgitation; AS = aortic stenosis; BSA = body surface area (m^2); CI = cardiac index (liters/min/m^2); ECD = endocardial cushion defect; HR = heart rate (beats/min); MR = mitral regurgitation; PaO_2 = arterial partial pressure of oxygen (mm Hg); PDA = patient ductus arteriosus; PS = pulmonary stenosis; SD = standard deviation; SI = stroke index (ml/m^2); SVR = systemic vascular resistance (Wood units); TAPVR = total anomalous venous return; TGS = transposition of the great arteries; VO_2 = oxygen consumption (ml/min/m^2); VSD = ventricular septal defect.

TABLE II Hemodynamic Effects of Breathing 95% Oxygen for 10 Versus 20 Minutes

	21% Oxygen							95% Oxygen												
								10 Minutes							20 Minutes					
Patient	HR	CI	SI	AoP	SVR	VO_2	PaO_2	HR	CI	SI	AoP	SVR	VO_2	PaO_2	HR	CI	SI	AoP	SVR	Vo_2	PaO_2
10	78	4.11	53	88	20	119	86	67	3.22	48	90	26	116	448	67	3.42	51	90	25	125	488
11	96	4.17	43	80	18	134	84	74	3.44	46	80	22	109	348	74	3.40	46	78	22	94	478
12	86	3.30	38	80	22	117	99	79	2.46	31	80	30	96	450	78	2.40	31	80	31	85	472
16	115	3.19	28	78	23	118	73	108	2.72	25	85	29	98	260	109	2.87	26	85	28	87	263
20	114	2.76	24	70	24	70	100	115	2.52	22	72	26	85	486	114	2.49	22	72	28	78	492
Mean	98	3.50	37	79	22	112	88	89	2.85	35	81	27	101	398	88	2.92	35	81.0	26	94	439
±SD	±16	±0.54	±12	±6	3	±24	±11	±22	±0.39	±12	±6	±3	±11	±93	±21	±0.43	±13	±7	±4	±18	±98
Significance*	...	...	...	...	...	...		...	...	...	...	...	...	...	NS	NS	NS	NS	NS	NS	†

* Compared with value in 95% oxygen for 10 minutes.
† $p < 0.05$.
NS = not significant at $p < 0.05$. Other abbreviations as in Table I.

Before catheterization, each patient was premedicated with morphine sulfate (0.15 mg/kg) and diphenhydramine (1.0 mg/kg). After right and left heart catheterization had documented the underlying lesion, and before angiography, the study was performed. Baseline hemodynamic variables were measured with the patient breathing room air. Heart rate was determined from the electrocardiogram and averaged over a 10-second period. Pressures were measured in the aorta, right atrium, pulmonary artery, and pulmonary artery wedge position. Aortic and pulmonary artery blood was sampled for blood gas (IL 813 analyzer) and oxygen saturation (reflection oximetry) measurements. All blood gas samples were collected in cold heparinized syringes, placed in ice, and analyzed within 5 minutes. Hemoglobin concentration was measured in an IL 182 co-oximeter, and oxygen-carrying capacity was calculated by multiplying the hemoglobin concentration by 1.36. CI was measured by thermodilution technique (IL 701 thermodilution computer) and taken as the average of 3 determinations. In 5 patients, CI was also measured by dye dilution technique. Oxygen consumption (VO_2) was measured using a continuous flow-through system in room air,[7] and was also calculated from thermodilution CI and oxygen content difference according to the Fick principle in both room air and 95% oxygen: VO_2 = thermal dilution cardiac output (10 × [oxygen capacity × aortic saturation + 0.003 × aortic PO_2]) − (oxygen capacity × pulmonary artery saturation + 0.003 × pulmonary artery PO_2), where PO_2 = partial pressure of oxygen. Core temperature was measured with thermodilution thermistor situated in the main pulmonary artery.

After acquisition of baseline data, each patient was administered 95% oxygen. This was the highest inspired oxygen concentration that could be reliably administered by a hood system. Inspired oxygen concentration (F_IO_2) was determined using an Applied Electrochemistry oxygen analyzer. Measurements of heart rate, pressures, blood gases and saturations, CI, and VO_2 were made as just described after oxygen breathing for 10 minutes (n = 26) and 20 minutes (n = 5). Hemodynamic measurements were then repeated with the patient once again breathing room air for 10 minutes (n = 11) and 20 minutes (n = 6).

To evaluate the hemodynamic significance of reflex bradycardia during oxygen breathing, heart rate was kept constant by atrial pacing (rate 5 beats/min above the spontaneous sinus rate) in 5 patients. Hemodynamic measurements were made in room air and after breathing 95% oxygen for 10 minutes as described previously.

Data were evaluated for significance using the two-tailed *t* test for paired observations. All values are expessed as mean ± standard deviation.

TABLE III Duration of Oxygen-Induced Hemodynamic Changes

	21% Oxygen (Baseline)						95% Oxygen (10 Minutes)					
Patient	HR	CI	SI	AoP	SVR	VO_2	HR	CI	SI	AoP	SVR	VO_2
10	78	4.11	53	88	20	119	67	3.22	48	90	26	116
12	86	3.30	38	80	22	117	79	2.46	31	80	30	96
14	96	4.39	46	70	15	145	94	3.58	38	72	19	123
18	85	4.53	53	90	19	175	96	4.10	43	95	22	92
22	135	3.91	29	85	21	123	140	3.21	23	88	26	85
25	143	2.39	17	85	31	182	126	1.54	12	77	43	99
2	124	1.91	15	91	47	159	125	1.79	14	98	51	126
5	120	4.79	30	83	16	173	105	4.48	43	84	18	...
16	115	3.19	28	78	23	118	108	2.72	25	85	29	98
17	107	3.75	35	72	17	147	102	3.30	31	80	22	134
19	116	3.92	34	90	22	113	96	3.35	35	90	25	80
21	85	4.39	52	70	15	143	77	3.15	41	77	22	96
Mean	107	3.71	37	82	22	143	101	3.07	32.0	85	28	104
±SD	±21	±0.83	±13	±8	±9	±25.1	21	±0.81	±11.4	±8	±10	±18
Significance*												

* Compared with baseline value in 21% O_2.
Abbreviations as in Table I.

Results

After 10 minutes of breathing 95% oxygen, mean arterial PO_2 increased from 86 ± 13 to 420 ± 89 torr ($p < 0.001$) and arterial oxygen content increased from 17.0 ± 1.9 to 18.7 ± 2.0 ml/100 ml ($p < 0.001$). There was a slight increase in these values after 20 minutes of oxygen breathing. The increase in mean arterial PO_2 to only (420 ± 89 torr) after 10 minutes of breathing 95% oxygen suggests that some degree of intrapulmonary right-to-left shunting was present in our patients. Arterial pH, PCO_2, and temperature did not change during the study.

Significant hemodynamic effects were noted after 10 minutes of oxygen breathing (Table I). Heart rate decreased from 103 ± 21 to 94 ± 22 beats/min ($p < 0.001$). Mean systemic arterial pressure increased from 80 ± 11 to 83 ± 10 mm Hg ($p < 0.01$), and mean pulmonary arterial pressure decreased from 24 ± 12 to 22 ± 11 mm Hg ($p < 0.01$). Mean right atrial pressure increased from 5 ± 2 to 6 ± 2 mm Hg ($p < 0.01$), while the small observed increase in pulmonary arterial wedge pressure from 10 ± 5 to 11 ± 5 mm Hg ($p = 0.15$) did not reach statistical significance.

CI measured by thermodilution technique was diminished in every patient after 10 minutes in 95% oxygen. Mean CI decreased by 21% from 3.96 ± 0.94 to 3.12 ± 0.74 liters/min/m^2 ($p < 0.001$). Stroke index decreased by 11% from 39.9 ± 11.1 to 35.5 ± 9.7 ml/m^2 ($p < 0.001$). In 5 patients, CI determined by dye dilution did not differ significantly from simultaneous thermodilution measurements.

Oxygen breathing resulted in a significant elevation of SVR from 20.1 ± 6.9 to 25.5 ± 7.7 U ($p < 0.001$). Pulmonary vascular resistance did not change significantly.

VO_2 was calculated from thermodilution cardiac output according to the Fick principle. In room air, this calculated VO_2 did not differ significantly from VO_2 measured by a continuous flow-through system (150 ± 26 versus 156 ± 24 ml/min/m^2, respectively). After 10 minutes of breathing 95% oxygen, VO_2 decreased by 24% ($p < 0.001$) (Table I). Oxygen transport, the product of arterial oxygen content and cardiac output, decreased as well, from 762.9 ± 179.4 to 600.2 ± 161.3 ml O_2/min/m^2 ($p < 0.001$).

After 20 minutes of oxygen breathing, no further hemodynamic changes were noted. The data in Table II indicate that hemodynamic measurements made after 20 minutes did not differ significantly from those made after 10 minutes of breathing 95% oxygen. Thus, oxygen seems to exert its major cardiovascular effects within 10 minutes. Ten minutes after cessation of oxygen breathing, however, all values had not returned to baseline (Table III). CI, stroke volume, oxygen transport, and VO_2 remained significantly depressed and SVR remained elevated ($p < 0.01$). These and all other hemodynamic parameters returned to normal after 20 minutes after oxygen breathing.

The effects of breathing 95% oxygen on the 5 patients with congestive heart failure are presented in the Figure 1. These data are highlighted since the hemodynamic effects of oxygen in such patients may be of particular clinical relevance. When compared with the 21 patients without failure, oxygen decreased CI and stroke volume and increased SVR in the 5 children with congestive failure. CI decreased from 2.95 ± 0.95 to 2.38 ± 0.79 liters/min/m^2 ($p < 0.05$), stroke index decreased from 28.1 ± 13.4 to 23.6 ± 11.1 ml/m^2 ($p < 0.05$), and SVR increased from 27.7 ± 11.8 to 34.0 ± 13.1 U ($p < 0.05$).

To evaluate the role played by reflex bradycardia during oxygen breathing, heart rate was held constant by atrial pacing in 5 patients. Hemodynamic values measured before oxygen and after breathing 95% oxygen for 10 minutes are presented in Table IV. CI and stroke index both decreased by 12% ($p < 0.05$). VO_2 also decreased from 146.2 ± 42.2 to 97.0 ± 12.0 ml/min/m^2 ($p < 0.05$). SVR increased in oxygen from 22.8 ± 5.1 to 26.4 ± 5.5 U ($p < 0.05$).

TABLE III (Continued)

	Return to 21% Oxygen											
	10 Minutes						20 Minutes					
Patient	HR	CI	SI	AoP	SVR	VO_2	HR	CI	SI	AoP	SVR	VO_2
10	79	3.88	49	100	...	118	...	...	...	...	...	...
12	92	2.80	30	80	26	110	...	...	...	...	...	...
14	96	3.91	41	70	17	130	...	...	...	...	...	...
18	94	4.26	45	90	18	148	...	...	...	...	...	...
22	142	4.24	30	100	22	133	...	...	...	...	...	...
25	137	1.80	13	72	...	134	...	...	...	...	...	...
2	...	...	...	...	...	...	130	1.93	15	90	45	164
5	116	3.60	31	66	16	118	120	4.79	40	66	12	157
16	112	2.76	25	78	26	102	115	3.19	28	78	23	124
17	107	3.51	33	72	18	145	107	3.85	36	72	16	159
19	105	3.38	32	90	26	108	110	3.75	34	90	23	120
21	84	3.64	43	66	17	124	85	4.33	51	68	14	148
Mean	106	3.43	33.8	80	21	124	111.2	3.64	34	77	22	145
±SD	±20	±0.69	±10.2	±13	±4.2	±15	±15.2	±0.84	±12.1	±11	±11.8	±19
Significance*	NS	†	‡	NS	†	‡	NS	NS	NS	NS	NS	NS

† $p < 0.01$.
‡ $p < 0.05$.

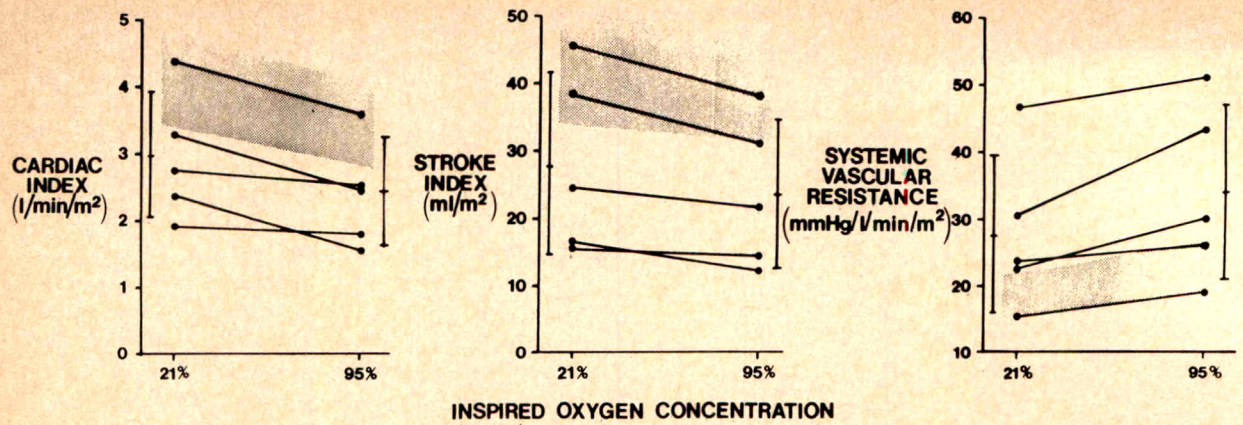

FIGURE 1. Cardiovascular effects of oxygen.

Discussion

This study documents significant hemodynamic changes induced by the breathing of 95% oxygen in children with congenital heart disease. Oxygen breathing increased SVR and arterial pressure, and decreased heart rate, CI, and stroke volume. A marked decrease in VO_2 was observed as well. These hemodynamic changes occurred in all patients regardless of cardiac diagnosis or the presence of intrapulmonary right-to-left shunting.

Several studies have documented an increase in SVR induced by hyperoxia.[1–6,8] Eggers et al[1] noted a 22% increase in 10 healthy adults breathing 100% oxygen for 20 minutes. Torbati et al,[5] studying rats exposed to high oxygen tension, concluded that the elevated SVR was due primarily to vasoconstriction in large muscle groups. This is consistent with observations, using venous occlusion plethysmography, that forearm blood flow is reduced by 18.9% in adults breathing oxygen at 2 atm pressure.[8] Hyperoxia has been shown to affect SVR by increasing precapillary sphincter tone.[9] The mechanism by which oxygen increases SVR remains unclear, however. A direct constrictor effect of oxygen on arteriolar smooth muscle and chemoreceptor-mediated reflex vasoconstriction have been postulated.[20] The observation that significant hemodynamic effects persist for 20 minutes (40 minutes in Egger et al's study[1]) despite normalization of arterial oxygen content suggests that a circulating vasoconstrictor substance may also be involved in mediating the cardiovascular response to hyperoxia.

A decrease in heart rate during oxygen breathing has also been reported by a number of investigators.[1–3,5,11,12] Daly and Bondurant[2] demonstrated an inverse linear relationship between heart rate and inspired oxygen concentration in 15 normal adults. After administration of atropine, however, heart rate did not decrease in response to high inspired oxygen concentrations. Thus, it appears that hyperoxia-induced bradycardia may be mediated by the baroreflex in response to an increase in arterial pressure.

CI decreases in response to hyperoxia.[1–6,13] Our data indicate that this is due to the combined effects of a decrease in both heart rate and stroke volume. CI decreased by 21% after 10 minutes of breathing 95% oxygen. In the 5 patients whose heart rates were kept constant by atrial pacing, CI decreased by 12%, entirely the consequence of a diminished stroke volume. This 12% decrease in stroke volume was almost identical in magnitude to that observed in the 26 nonpaced patients.

TABLE IV Hemodynamic Effects of Breathing 95% Oxygen in 5 Children During Atrial Pacing

			21% Oxygen (Baseline)								95% Oxygen (10 Minutes)							
Patient	Diagnosis	Age (yr)	HR	CI	SI	AoP	SVR	VO_2	PaO_2	$PaCO_2$	HR	CI	SI	AoP	SVR	VO_2	PaO_2	P_aCO_2
27	Mustard repair of D-TGA	2.0	85	3.24	38	68	20	132	94	39	85	2.80	33	80	27	90	480	37
28	VSD repair	12.0	105	3.48	33	97	26	97	98	38	105	3.32	32	108	29	85	390	38
29	TOF repair	5.0	125	4.71	38	97	20	213	96	33	125	3.91	31	93	23	103	420	35
30	VSD repair	10.0	95	3.50	37	115	30	140	88	38	95	2.93	31	110	33	91	391	39
31	VSD repair	1.4	115	3.48	30	69	18	149	68	42	115	3.30	29	72	19	115	248	44
Mean	...		105	3.68	35	89.2	23	146	89	38	105	3.25	31	93	26	97	386	39
±SD			±16	±0.59	±3	±20.3	±5	±42	±12	±3	±16	±0.43	±2	±17	±6	±12	±85	±3
Significance*	...		...	...	...	...	...	...	...	...	NS	†	†	NS	†	†	†	...

* Compared with baseline value in 21% O_2.
† $p < 0.05$.
NS = not significant at $p < 0.05$.
Abbreviations as in Table I.

Thus, the decrease in CI during oxygen breathing is due to a decrease in stroke volume as well as heart rate. In contrast, Daly and Bondurant[2] failed to demonstrate a statistically significant decrease in stroke volume in 6 patients during oxygen breathing when reflex bradycardia was abolished by atropine administration. Their data show, however, that stroke volume did decrease in 4 subjects and was unchanged in 2.

The oxygen-induced decrease in stroke volume may be due to multiple factors. First, it may reflect an increased SVR and left ventricular afterload. This factor may be of particular significance in children with heart disease. Second, the decrease in stroke volume may relate to myocardial depression by hyperoxia. Several studies have documented diminished ventricular function in animals exposed to high oxygen concentrations.[10–16] Kioschos et al,[15] for example, found a 14% decrease in the first derivative of left ventricular pressure in dogs during hyperbaric oxygenation at 3.6 atm for 15 minutes. Finally, hyperoxia has been shown to decrease coronary artery blood flow,[14,17] which may further compromise myocardial function.

The hemodynamic response to hyperoxia may be of particular clinical relevance in children with congestive heart failure and already compromised ventricular performance. Figure 1 illustrates some of the hemodynamic changes induced by breathing 95% oxygen for 10 minutes in 5 children with heart failure. In room air, these children already had a mean CI and stroke index well below, and a mean SVR well above the group as a whole. Nevertheless, oxygen administration caused a further 19% decrease in CI and 16% decrease in stroke index. SVR resistance increased by 23% from 27.7 to 34 units. These potentially adverse hemodynamic effects were noted in each child after 10 minutes of oxygen administration.

In the present study, VO_2 decreased by 25% after 10 minutes in 95% oxygen. A similar marked decrease in VO_2 has been reported during hyperbaric oxygenation.[13] The mechanisms involved are unknown but one can speculate that peripheral vasoconstriction and decreased cardiac output may cause underperfusion of metabolizing tissues. In fact, the present data have shown that oxygen transport, the volume of oxygen delivered to the tissues each minute, is depressed by hyperoxia. Oxygen in high concentration may also directly inhibit oxidative metabolism. In rabbits exposed to oxygen at 3 atm a marked lactic acidosis develops, supporting the concept that aerobic metabolism is inhibited by hyperoxia.[18]

The present study has a number of potential clinical implications. First, at cardiac catheterization it is common to assess the hemodynamic response to oxygen breathing of patients with intracardiac shunts or pulmonary vascular obstructive disease. Our findings suggest that pulmonary blood flow may be overestimated and pulmonary resistance underestimated if one assumes that oxygen consumption in oxygen is the same as that measured in room air. Second, the medical and surgical therapy of children with acyanotic heart disease often includes administration of oxygen in the range of inspired oxygen concentration of 30 to 50%. Thus, further investigations are warranted to determine if similar adverse hemodynamic changes occur when these therapeutic concentrations of oxygen are given.

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Altered Baroreceptor Function in Children With Systolic Hypertension After Coarctation Repair

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To determine whether altered baroreceptor function may contribute to systemic hypertension after coarctation of the aorta (C of A) repair, baroreceptor function was evaluated in 6 children with repaired C of A mild arm systolic hypertension. Data were compared with those from 7 normotensive control children with hemodynamically mild heart disease. Age at C of A repair averaged 9.9 ± 3.1 years (mean ± standard deviation [SD]). Arm systolic pressure was 143.8 ± 2.9 mm Hg in the C of A repair group, compared with 118.3 ± 9.9 for control subjects ($p < 0.001$). At catheterization, steady-state sigmoidal baroreceptor function curves relating mean arterial pressure to R-R interval were derived by increasing and decreasing mean arterial pressure with small injections of phenylephrine and nitroprusside. Compared with control subjects, the baroreceptor function curves of children with repaired C of A (1) are reset about a higher baseline mean arterial pressure (108.8 ± 6.6 versus 90.3 ± 8.6 mm Hg, $p < 0.01$), (2) have a decreased slope (7.9 ± 3.7 versus 17.4 ± 3.6 ms/mm Hg, $p < 0.001$), and (3) have a diminished R-R interval range (246.7 ± 81.5 versus 535.7 ± 97.2 ms, $p < 0.001$). Thus, in children with hypertension after C of A repair, the baroreflex is reset to an elevated mean arterial pressure level and has a diminished sensitivity to changes in arterial pressure.

Arm hypertension, at rest or during dynamic exercise, occurs frequently after repair of coarctation of the aorta (C of A).[1–5] In some patients, hypertension is clearly related to a residual or recurrent C of A.[6] In others, however, those with little or no residual resting C of A gradient, the cause of postoperative hypertension is less clear. The baroreflex is intimately involved in blood pressure regulation, but its function in patients with repaired C of A has not been evaluated. Nevertheless, studies in dogs with experimental C of A[7,8] have documented baroreflex alterations similar to those described in adults with chronic essential hypertension.[9–11] The purpose of this study is to evaluate baroreceptor function in children with repaired C of A who have mild arm hypertension.

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Methods

Six children, 5 boys and 1 girl, with good surgical repair of C of A (resting peak systolic gradient of <25 mm Hg) and mild resting arm systolic hypertension (>140 mm Hg) served as subjects of this investigation. A group of 7 normotensive children with hemodynamically mild heart disease served as control subjects. Pertinent clinical and hemodynamic data are presented in Table I. The children with repaired C of A ranged in age from 13.8 to 19.0 years, averaging 16.8 ± 2.0 years (mean ± SD). The control children averaged 15.4 ± 4 years of age, which is not significantly different from that in the C of A repair group. The 6 children with repaired C of A had undergone repair of a discrete thoracic C of A at an average age of 9.9 ± 3.1 years (range 6.8 to 13.8). Before C of A repair, all children had resting arm hypertension (defined as systolic pressure at or above the 95th percentile for age and sex) averaging 146.8 ± 16.2 mm Hg. C of A repair was performed by end-to-end anastomosis in 4 children (Patients 3 to 6) and by patch aortoplasty in 2 (Patients 1 and 2). Immediately after surgical repair, 5 children (Patients 1, 2, 3, 5, and 6) had paradoxical hypertension requiring vigorous antihypertensive therapy for 2 to 3 days. The interval from repair to the present study averaged 6.9 ± 3.7 years. At the time of this study, no patient was receiving antihypertensive medication or digoxin. There were no associated hemodynamic lesions of significance. One patient (Patient 4) had also undergone repair of a ventricular septal defect with excellent

TABLE I Pertinent Clinical Data in 6 Children With Repaired Coarctation and 7 Control Children

Patient	Diagnosis	Age (yr)	Age at C of A Repair (yr)	Resting Outpatient Data: HR (beats/min)	Rt Arm BP (mm Hg) Syst	Rt Arm BP (mm Hg) Dias	Rt Arm-Rt Leg Syst Gradient (mm Hg)	Treadmill Exercise: HR Peak Ex (beats/min)	Rt Arm Systolic Pressure (mm Hg) Post Ex	C of A Gradient (mm Hg) Post Ex
Coarctation Repair										
1	Patch aorto-plasty	13.8	12.9	93	142	82	8	184	206	32
2	Patch aorto-plasty	18.2	13.8	76	145	70	6	202	210	86
3	End-to-end anasto-mosis	14.4	6.8	81	141	60	7	198	240	90
4	End-to-end anasto-mosis	19.0	11.9	85	146	80	0	182	220	40
5	End-to-end anasto-mosis	17.1	6.8	76	141	70	28	188	230	120
6	End-to-end anasto-mosis	18.3	7.2	71	148	85	2	189	234	83
Mean		16.8	9.9	80.3	143.8	74.5	7.8	190.5	223.3	75.2
±SD		±2.0	±3.1	±7.8	±2.9	±9.4	±10.6	±7.9	±13.6	±33.2
p value*		NS	...	NS	<0.04	NS	<0.05	NS	<0.001	...
Controls										
7	PS, mild	14.0	...	84	115	76	−2	...	...	...
8	TOF repair PS, mild	19.0	...	74	125	78	0	178	168	...
9	PS, mild	20.2	...	90	136	75	−2	...	...	...
10	PS, trivial	13.7	...	75	112	60	−5	200	144	...
11	AS, mild	13.6	...	82	108	78	0	188	140	...
12	VSD repair	19.5	...	78	122	76	−2	180	140	...
13	AS, trivial	8.1	...	95	110	73	1	170	141	...
Mean		15.4	...	83	118	74	−1.4	183	147	...
±SD		±4	...	±8	±10	±6	±2.0	±11	±12	...

* Coarctation repair group versus control group.
AS = aortic stenosis; AsAo = ascending aorta; C of A = coarctation of aorta; DescAo = descending aorta; dias = diastolic; HR = heart rate; NS = not significant at $p < 0.05$; PS = pulmonic stenosis; Rt = right; SD = standard deviation; syst = systolic; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

results, and another (Patient 6) had trivial mitral insufficiency. No patient had aortic insufficiency or aberrant right subclavian artery.

Outpatient blood pressure was measured by auscultation in the right arm and by the use of a Doppler flow probe over the posterior tibial artery. Blood pressure cuffs of appropriate size, covering at least two thirds of the limb, were used on the right upper arm and calf. All reported blood pressure values are the average of at least 3 measurements.

Dynamic exercise testing was performed on a motorized treadmill according to the Bruce protocol.[12] All children exercised to physical exhaustion defined as inability to exercise further despite vigorous encouragement from the staff to do so. Leads II, aVF, and V_5 were recorded throughout the exercise study. Blood pressure was measured by auscultation in the right arm and by the use of a Doppler flow probe over the posterior tibial artery. Blood pressure cuffs of appropriate size, covering at least two thirds of the limb, were used on the right upper arm and calf. Simultaneous supine arm and leg blood pressure measurements were made at rest (reported values are the average of at least 3 measurements) and within 30 seconds after the conclusion of exercise.

After obtaining informed consent, all patients underwent cardiac catheterization to evaluate their coarctation repair site and to determine a possible explanation for their resting and exercise hypertension.

During diagnostic cardiac catheterization, resting baroreceptor function was evaluated in each patient before angiography. All patients received light sedation with morphine sulfate (0.1 mg/kg, maximum 5 mg) and diphenhydramine (1 mg/kg, maximum 50 mg). The R-R interval was measured directly from lead II of the electrocardiogram, recorded at a paper speed of 100 mm/s. Arterial pressure was recorded from a catheter situated in the aortic arch proximal to the site of C of A repair. Mean arterial pressure (MAP) was determined by electronic damping and was recorded, together with phasic arterial pressure, continuously throughout the study. Incremental changes in MAP were produced by injection (over 10 to 15 seconds) into the inferior vena cava of small doses of phenylephrine (50 to 150 μg) and nitroprusside (25 to 50 μg). Each drug was diluted in 0.9% sodium chloride and the total volume of each injection never exceeded 4 ml. In each subject, 3 or 4 doses each of phenylephrine and nitroprusside were administered to produce small (10%) to moderate (25%) increases and decreases in MAP. Three- to 5-minute intervals were taken between each drug injection to allow MAP and R-R interval to return to baseline levels. After each drug injection, MAP and R-R interval increased or decreased within

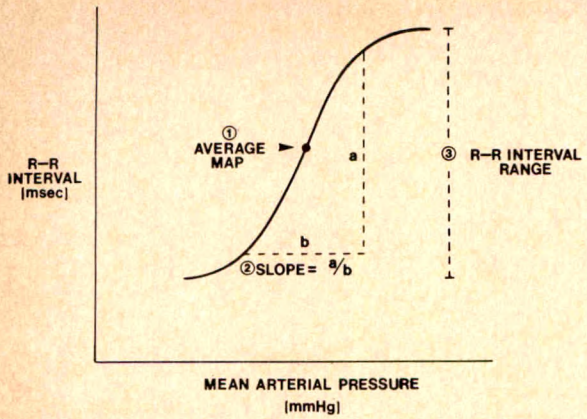

FIGURE 1. Idealized baroreceptor function curve. The curve is characterized by 3 parameters: (1) average baseline mean arterial pressure (MAP); (2) slope (a/b); and (3) R-R interval range.

15 seconds to a new plateau level which was sustained for 10 to 20 seconds. MAP was measured at baseline before, and at the plateau after each injection. The R-R interval was also measured at each baseline and plateau and the values reported represent the average of 3 consecutive R-R interval measurements. The range of MAP over which baroreceptor function was studied was comparable in the C of A repair and control group averages of 42.2 ± 2.7 mm Hg and 44.1 ± 2.9 mm Hg, respectively ($p = 0.61$).

Steady-state baroreceptor function curves were then constructed for each child by relating each R-R interval to its corresponding MAP value. Sigmoidal curves were constructed using the cumulative standard normal distribution function (ϕ)*. This sigmoidal function was utilized since previous studies have shown that the baroreceptor function curve is sigmoidal in nature.[11] Each patient's baroreceptor function curve was defined by the following equation: $RR = A + B\,\phi(MAP - \overline{MAP})/SD_i$, where i represents phenylephrine or nitroprusside, RR represents each R-R interval, and MAP each corresponding MAP value. $\overline{MAP}$ is the average baseline MAP for the patient. SD represents the standard deviation for each patient of the MAP values measured after drug injections either with phenylephrine or nitroprusside. Since the relationship between R-R interval and mean arterial pressure has been shown to be characterized by an asymmetric sigmoid curve,[11] 2 different standard deviations were used in constructing the upper and lower portions of the curve, respectively—one for the MAP values greater than $\overline{MAP}$ (that is, after phenylephrine) and another for the $\overline{MAP}$ values less than MAP (such as after nitroprusside). This procedure permitted each curve to be asymmetrical if warranted by the data. A separate A and B were determined for each subject using least-squares linear regression, since data within subjects were correlated.

Each patient's baroreceptor function curve was characterized by 3 parameters: (1) average baseline MAP, (2) slope, and (3) R-R interval range. Figure 1 depicts an idealized baroreceptor curve with these 3 parameters indicated. Average baseline MAP ($\overline{MAP}$) is the average of all MAP values at baseline before each drug injection, and represents the set-point pressure about which the baroreflex operates. The slope of a baroreceptor function curve is an index of baroreflex sensitivity to changes in arterial pressure. In this study the reported slope is the average slope of the linear portion of the curve over a pressure range defined as $\overline{MAP} \pm 1$ SD (standard deviation for each patient of all the MAP values measured after drug injections). For example, in Figure 1 the slope is a/b, where b represents $\overline{MAP} \pm 1$ SD. The R-R interval range is the difference between the R-R interval at the upper and lower plateaus of the baroreceptor function curves. This represents the R-R range over which the baroreflex operates.

Descending aortic angiograms were obtained on all 6 C of A patients. The descending thoracic aorta at the C of A repair site and at the level of the diaphragm were measured using calibrated grids. In the 7 control patients, the descending thoracic aorta was measured from either the levophase of a right ventricular angiogram or from a left ventricular angiogram.

Statistical significance was assessed using Student's t test. Group values are reported as mean ± standard deviation.

Results

Arm systolic pressure at rest averaged 143.8 ± 2.9 mm Hg for the 6 children with repaired C of A (Table I). This ranks in the 90th percentile for systolic pressure according to the National Heart, Lung, and Blood Institute's blood pressure charts for children.[13] Resting systolic pressure was significantly lower in the control group, averaging 118.3 ± 9.9 mm Hg ($p < 0.05$). Resting diastolic pressure was normal in both groups, averaging 74.5 ± 9.4 mm Hg and 73.7 ± 6.2 mm Hg in the C of A repair and control groups, respectively. The C of A pressure gradient at rest averaged 7.8 ± 10.6 mm Hg in the 6 children with repaired C of A. There was no significant difference between study and control patients with regard to resting heart rate. All children with repaired C of A had an abnormal blood pressure elevation in response to treadmill exercise (Table I). Upper extremity systolic pressure, measured immediately after exercise, averaged 223.3 ± 13.6 mm Hg in the coarctation repair group, compared with 146.6 ± 12.1 mm Hg for the control group ($p < 0.001$). There was no overlap of postexercise systolic pressure between the 2 groups. The coarctation pressure gradient increased to 75.2 ± 33.2 mm Hg immediately after exercise. Arm diastolic pressure immediately after exercise was not significantly different in the coarctation repair and control groups, averaging 73.5 ± 15.2 mm Hg and 66.6 ± 17.8 mm Hg, respectively. Maximal heart rate attained at peak exercise was also similar in the 2 groups. At cardiac catheterization, all children appeared to have a good hemodynamic repair of C of A, with peak systolic gradients from ascending to descending aorta ranging from 0 to 20 mm Hg (mean 8.5 ± 7.3 mm Hg) (Table II). In all 6 patients, aortograms demonstrated a mild indentation of the descending aorta at the site of coarctation repair. However, in no patient was this residual narrowing <70% of the size of the descending aorta at the level of the diaphragm (Table II).

Baroreceptor function, as defined by the steady-state relationship between mean arterial pressure and R-R interval, was significantly different in the children with repaired C of A compared with control children. Figure 2 illustrates representative baroreceptor function curves of a child with repaired C of A and a control child. The

*$\phi(y) = \int_{-\infty}^{y} \frac{1}{\sqrt{2\pi}} e^{-x^2/2}\,dx$, where $y = (MAP - \overline{MAP})/SD$

TABLE II Pertinent Cardiac Catheterization in 6 Children With Repaired C of A and 7 Control Children

Patient	HR (beats/min)	AsAo Pressure (mm Hg)			DescAo Pressure (mm Hg)			Size of Residual Narrowing (mm)	Size Descending Ao at Diaphragm (mm)
		Syst	Dias	Mean	Syst	Dias	Mean		
				Coarctation Repair					
1	96	153	101	117	150	100	117	14.4	15.7
2	84	128	83	97	123	80	97	15.3	19.4
3	76	148	82	100	138	80	99	11.8	15.9
4	80	145	80	100	145	80	100	16.6	21.4
5	78	138	78	97	118	76	89	10.0	14.0
6	72	142	78	100	129	76	96	12.5	17.8
	81	141.1	83.6	101	132.6	82	99.6	13.4	17.4
	±8.4	±9.3	±8.7	±7.5	±14	±9	±9.3	±2.4	±2.7
	NS	<0.05	NS	p <0.01	NS	NS	NS	. . .	NS
				Control					
7	84	112	70	83	120	70	82	. . .	13.7
8	72	110	71	82	108	71	81	. . .	17.3
9	93	125	78	93	130	77	94	. . .	19.6
10	89	112	72	85	118	72	85	. . .	16.7
11	82	118	74	88	120	73	88	. . .	13.4
12	69	98	62	84	100	62	84	. . .	17.4
13	88	123	88	99	123	88	99	. . .	13.2
	82.4	114	73.5	87.7	117	73.3	87.5	. . .	15.9
	±8.9	±9.1	±8.0	±6.2	±9.9	±7.9	±6.6	. . .	±2.5

Grad = gradient; other abbreviations as in Table I.

data describe sigmoidal curves with well-defined slopes in the mid-portion of the curves and clear upper and lower plateaus. Table III lists the baroreceptor function curve characteristics for the 2 groups of children. The average baseline mean arterial pressure ($\overline{MAP}$) was 108.8 ± 6.6 mm Hg for the repaired C of A group compared with 90.4 ± 8.6 mm Hg for the control group ($p < 0.01$). Thus, the baroreflex has been reset to operate at high arterial pressure levels in the children with repaired C of A. The baroreceptor function curves of the children with repaired C of A have diminished slopes compared with control curves. In these children, the slope averages 7.9 ± 3.7 ms/mm Hg, compared with 17.4 ± 5.1 ms/mm Hg in the control group ($p < 0.001$), a 55% difference. This indicates diminished baroreflex sensitivity to changes in arterial pressure in the children with repaired C of A. Finally, the R-R interval range averages 246.7 ± 81.5 ms in the C of A repair group compared with 535.7 ± 97.2 ms in the control group ($p < 0.001$). Figure 3 illustrates the composite baroreceptor

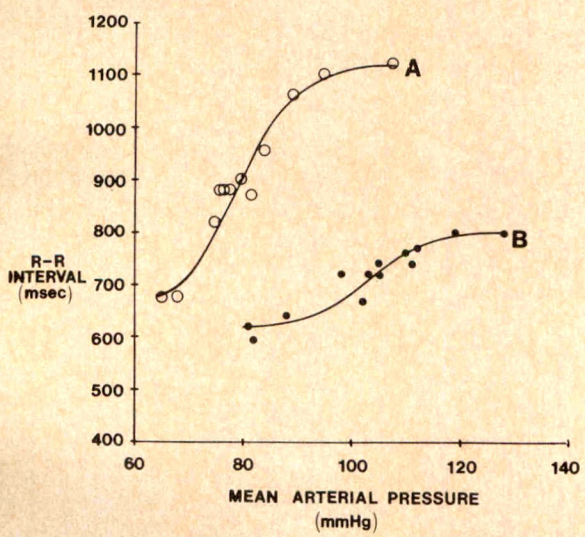

FIGURE 2. Representative individual baroreceptor function curves. A = curve of control, Patient 12. B = curve of coarctation repair, Patient 2.

TABLE III Baroreceptor Function Curve Characteristics in Children With Repaired Coarctation and in Control Children

Patient	MAP (mm Hg)	Slope (ms/mm Hg)	R-R Interval Range (ms)
	Coarctation Repair		
1	121	5.2	230
2	104	7.0	240
3	110	6.5	170
4	110	8.7	320
5	104	5.1	160
6	104	14.8	360
Mean	109	7.9	246.7
±SD	7	±3.7	±81.5
p value*	<0.01	<0.001	<0.001
	Controls		
7	90	17.4	590
8	86	10.1	390
9	95	20.9	550
10	88	17.0	700
11	96	19.7	530
12	80	16.4	450
13	98	20.3	540
Mean	90	17.4	536
±SD	9	3.6	97

* Compared with control values.
MAP = average baseline mean arterial pressure; other abbreviations as in Table I.

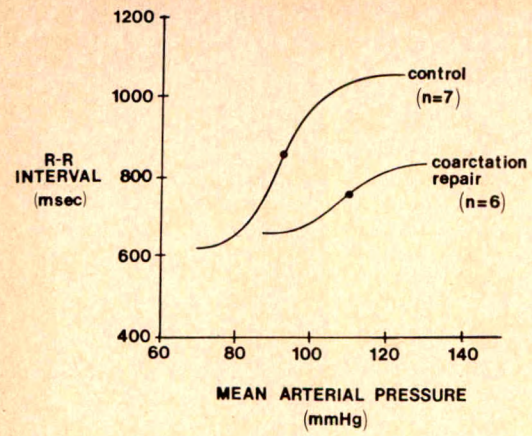

FIGURE 3. Composite baroreceptor curves of children with repaired coarctation and control children. The curves clearly differ in regard to average baseline MAP, slope, and R-R interval range.

function curves of the 6 children with repaired C of A and the 7 control children. These curves were constructed with the standard formula using averaged MAP, A, B, and SD (square root of averaged individual variances) values for the 2 groups. The two composite baroreceptor curves are clearly different. The C of A repair curve has been reset to a higher average baseline MAP and has a diminished slope compared with the control curve. The decrease in R-R interval range of the C of A repair curve is shown to be due to a lowering of the upper R-R interval plateau, indicating a diminished bradycardiac response to arterial pressure elevation.

Baseline arterial pulse pressure was higher in the children with repaired C of A than in the control children, averaging 58.6 ± 8.4 mm Hg and 40.4 ± 4.2 mm Hg, respectively ($p < 0.05$). After injection of phenylephrine or nitroprusside, however, the changes in pulse pressure were not significantly different between groups. The baroreceptor characteristics discussed above are not corrected for baseline pulse pressure differences. An adjustment for differences in pulse pressure would further increase the discrepancy in baroreceptor function between the 2 groups, since baroreflex sensitivity is known to be enhanced by increased pulse pressure.[14]

Discussion

The present study has documented altered baroreceptor function in a group of children with repaired C of A who have mild arm systolic hypertension. In these children the baroreflex is reset to operate at higher arterial pressure levels and has a reduced sensitivity to changes in arterial pressure compared with control children. The diminished baroreceptor sensitivity (slope) was marked, averaging only 45% of the control value. In addition, the baroreceptor curve of the C of A repair group had a reduced R-R interval plateau, due almost entirely to a decrease in the upper R-R interval plateau. The level of the upper R-R interval plateau is dependent upon the degree of vagal efferent excitation and cardiac sympathetic inhibition, while the lower R-R interval plateau is determined by the degree of sympathetic excitation and vagal inhibition. We do not know which cardiac effector mechanism is altered in the children with repaired C of A but, based on studies of hypertensive adults,[11] the reduced upper R-R interval plateau seems more likely due to impaired vagal excitation than to impaired sympathetic inhibition.

The findings of the present study are similar to those of previous studies reporting altered baroreceptor function in adults with chronic essential hypertension.[9–11] Korner et al,[11] using a technique similar to ours to characterize steady-state baroreceptor function, also showed resetting, reduced baroreflex sensitivity, and a diminished R-R interval range in adults with chronic hypertension. In Korner's study the baroreceptor curve slopes of adults older than 30 years with severe resting hypertension (average MAP 151 mm Hg) averaged 11 ms/mm Hg compared with 21 ms/mm Hg for age-matched control subjects. These findings are quantitatively very similar to those of the present study. It is, however, important to note that although the technique of measuring heart rate response to injections of pressor and depressor drugs free of cardiac action is the most widely used test of baroreflex function in human subjects, it has the limitation of being unable to directly measure the baroreflex control of the peripheral circulation. Despite this, with the exception of denervation of either the carotid sinus or aortic arch baroreceptors,[14] most studies in both man[15] and animals[14,16,17] have demonstrated that with intact afferents there is a positive correlation between the heart rate and the arterial pressure responses to a baroreceptor manipulation. Thus, although we have only documented an abnormal heart rate response to baroreceptor stimulation in our children after C of A repair, we feel that it is likely that an abnormality of baroreceptor regulation of vascular resistance is also present.

Baroreceptor function has not previously been evaluated in children or adults with C of A. Two previous studies have, however, demonstrated altered baroreceptor function in dogs with experimental coarctation. Bonchek et al[7] reported resetting of the baroreflex to a higher pressure level, but normal reflex sensitivity, in 10 Labrador puppies with surgically created C of A. More recently, Igler et al[8] described both resetting and diminished baroreflex sensitivity in dogs with C of A studied under nonpulsatile flow conditions. Baroreceptor function was found to be normal after surgical repair of the experimental C of A.

The cause of altered baroreceptor function in hypertension has not been clearly elucidated. Although either the afferent or efferent limb of the reflex may be involved, most investigators have suspected that the changes reside in the afferent limb. Support for this view is found in animal studies, using single or multifiber preparations from the aortic and carotid sinus nerves, which have demonstrated an elevated threshold pressure (the pressure at which distinct nerve discharge first begins), an elevated saturation pressure (the pressure at which nerve firing no longer increases with increased pressure), and a decreased sensitivity (slope

of the stimulus-response curve over its linear range).[8,18,19] Such diminished baroreceptor responsiveness to elevated arterial pressure may involve 1 or more mechanisms. First, diminished baroreceptor function in hypertension may involve dysfunction of the afferent neuronal baroreceptor fibers themselves. Generalized destruction or inactivation of these receptor fibers could, in theory, depress baroreflex sensitivity. Angell-James[19] has presented histologic evidence of baroreceptor degeneration in the aortic arch of hypertensive rabbits. Similar findings in hypertensive persons have also been reported.[20] Second (and a more likely mechanism), with chronic hypertension, medial hypertrophy, elastic fiber degeneration, atherosclerosis, and changes in vessel sodium and water content may develop. These changes in the arterial wall may all act to diminish arterial wall compliance and thereby depress the baroreflex.[21] In addition to the effects of chronic hypertension, morphologic arterial wall abnormalities may occur in patients with coarctation which may further decrease vessel compliance.[22–24] Specifically, Sehested et al[24] have demonstrated, both by in vitro stimulation of aortic tissue from patients with C of A and by morphologic analysis, that the precoarctation aortic wall is more rigid and contains significantly more collagen and less smooth muscle than the postcoarctational wall. They speculated[24] that this reduced distensibility may influence baroreceptors in the upper vascular bed in such a way as to tolerate a higher pressure.

The findings of the present study suggest but do not prove that there may be a relationship between the observed abnormality in baroreceptor function and the presence of both resting and exercise hypertension in children with repaired C of A. There is no unanimity in the literature with regard to either the relationship between diminished baroreflex gain and hypertension[25,26] or the ability of the baroreflexes to modify the cardiovascular response to exercise.[27–30] Floras et al[27] demonstrated that adults with abnormal baroreflexes respond to a standard exercise test with a greater increase in blood pressure than that observed in adults with normal baroreflexes. Although altered baroreceptor function may contribute to both the maintenance of resting hypertension and the development of exercise hypertension after successful repair of C of A, we feel that it is not the major cause of the hypertension. Probably more important other causes include the magnitude[24] and duration[1] of preoperative hypertension, the mild residual narrowing of the descending thoracic aorta that is usually present after C of A repair,[5] and the possible decreased distensibility of the ascending aortic wall.[24] Studies of the baroreceptor function in children with repaired C of A who have normal resting and exercise blood pressure would help to clarify these relationships.

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Two-Dimensional Echocardiographic Assessment of Caval and Pulmonary Venous Pathways After the Senning Operation

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This study reports the 2-dimensional echocardiographic appearance of the caval and pulmonary venous pathways after the Senning procedure in 28 patients and establishes normal values for the caval and pulmonary venous pathway dimensions. Eighteen patients had no caval or pulmonary venous obstruction or tricuspid regurgitation at catheterization; 2 had isolated superior vena caval obstruction, 3 had isolated pulmonary venous obstruction, 4 patients had severe tricuspid regurgitation, and 1 had a large residual ventricular septal defect. The caval and pulmonary venous pathways were imaged in modified 4-chamber and transverse views, and the narrowest dimension of each pathway in each view was measured by 2 independent observers. Dimension measurements were then normalized to the cube root of body surface area. Caval and pulmonary venous pathway "dimension products" were obtained by multiplying the normalized dimension in the 4-chamber view by the normalized dimension in the transverse view.

All patients with catheterization-proven caval or pulmonary venous obstruction or tricuspid regurgitation had caval or pulmonary venous pathway dimension products outside the normal range, defined by our measurements in the 18 patients with no caval or pulmonary venous obstruction or tricuspid regurgitation. Thus, 2-dimensional echocardiography can provide both quantitative and qualitative information about the caval and pulmonary venous pathways after the Senning procedure.

Obstruction of either pulmonary or systemic venous return is the most common hemodynamic complication of the Senning procedure for d-transposition of the great arteries with intact ventricular septum.[1–4] When ventricular septal defect closure is combined with the Senning procedure as treatment for d-transposition of the great arteries with ventricular septal defect or for double-outlet right ventricle with subpulmonary ventricular septal defect and no subpulmonary stenosis, tricuspid regurgitation (TR) is an additional possible hemodynamic complication. A noninvasive technique[5] for evaluating the venous pathways would be desirable not only as a means of diagnosing obstruction or atrioventricular valve regurgitation, but also as a safe, convenient method for obtaining longitudinal data on the dimensions of the atrial compartments after the Senning procedure. To date, only a few centers have reported late postoperative catheterization data on survivors of the Senning procedure.[2–4,6] The prevalence of late development of systemic or pulmonary venous obstruction or TR will influence whether an atrial baffle operation such as the Senning procedure remains a viable surgical choice for transposition of the great arteries. Concerns about the development of supraventricular dysrhythmias,[7] atrial dysfunction,[8] and right ventricular dysfunction have already led some surgeons to abandon atrial baffle operations in favor of the arterial switch.[9,10] This study reports the 2-dimensional

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TABLE I Hemodynamic Data in 18 Patients with d-Transposition of the Great Arteries but Without Significant Residua After the Senning Procedure

Patient	Age (mo) at Cath	Time After Op (mo)	Other Preoperative Diagnosis	Catheterization Data: SVC-Neo RA Grad	IVC-Neo RA Grad	PCWa-RVEDP Grad	TR
1	15	12	0	0	0	0	0
2	19	13	0	1	0	0	0
3	20	17	Mal VSD	NA	NA	0*	+(mild)
4	19	11	0	2	1	2	0
5	19	12	0	0	0	0	0
6	12	12	0	1	0	0†	0
7	13	12	LAM	2	0	0	0
8	38	15	0	1	0	3†	0
9	52	12	Fixed SPS	NA	NA	2*	0
10	14	14	0	0	0	3	0
11	13	12	0	2	1	2†	0
12	19	19	0	4	1	1*	0
13	33	26	0	1	3	0*	0
14	8	8	0	1	1	0†	0
15	26	15	Memb VSD	1	0	4	0
16	17	13	Mal VSD	1	2	0	0
17	18	12	0	0	0	0	0
18	3 weeks	2 days	0	0	1	0	—

* Measured proximal neo-left atrium to distal neo-left atrium.
† Measured pulmonary capillary wedge mean pressure to right ventricular end-diastolic pressure.
Cath = catheterization; Grad = pressure gradient in mm Hg; IVC = inferior vena cava; LAM = left atrial membrane; Mal VSD = malalignment ventricular septal defect; Memb VSD = membranous ventricular septal defect; NA = not available; neo RA = neo-right atrium; Op = operation; PCWa = pulmonary capillary wedge a wave; RVEDP = right ventricular end-diastolic pressure; SPS = subpulmonary stenosis; SVC = superior vena cava; TR = tricuspid regurgitation.

(2-D) echocardiographic appearance of the caval and pulmonary venous pathways after the Senning procedure and establishes normal values for caval and pulmonary venous pathway dimensions.

Methods

Between July 1, 1979, and March 30, 1982, 28 patients (aged 3 weeks to 4 4/12 years, median 14 months) with d-transposition of the great arteries and intact ventricular septum (20),

TABLE II Cardiac Catheterization Data in 10 Patients With Hemodynamic Abnormalities After the Senning Procedure

Patient	Age (mo) at Cath	Time After Op (mo)	Preoperative Diagnosis	Catheterization Data: SVC-Neo RA Grad (mm Hg)	IVC-Neo RA	PCWa-RVEDP	TR	Other
Group II: Isolated SVC Obstruction								
19	1	2 Weeks	dTGA	10	1	2*	0	0
20	3	3 Days	dTGA	7	4	2	—	0
Group III: Isolated Pulmonary Venous Obstruction								
21	14	7	dTGA	1	NA	7	0	0
22	20	13	dTGA	0	0	7†	0	0
23	6	6	dTGA	4	1	20‡	—	0
Group IV: Severe Tricuspid Regurgitation								
24	4	1	dTGA, AVC-type VSD	1	2	3*	Severe	L→R vent shunt (Qp/Qs = 1.7)
25	12	2	DORV, PAB + coarc repair	1	1	0†	Severe	L→R atrial shunt (Qp/Qs = 1.9)
26	39	34	dTGA, AVC-type VSD	1	0	3	Severe	L→R vent shunt (Qp/Qs = 2.4)
27	7	4	dTGA, memb +2 musc VSD	7	4	1	Severe	L→R atrial shunt (Qp/Qs = 1.8)
Group V: Large Residual Ventricular Septal Defect								
28	7	3 Weeks	DORV, subpulm VSD, OMV	3	2	0	mild	L→R vent shunt (Qp/Qs = 2.8) (PPA = 3/4 systemic)

* Measured pulmonary capillary wedge mean pressure to right ventricular end-diastolic pressure.
† Measured proximal neo-left atrium to distal neo-left atrium.
‡ Measured pulmonary capillary wedge mean pressure to distal neo-left atrium.
AVC-type = atrioventricular canal type; coarc = coarctation; DORV = double-outlet right ventricle; dTGA = d-transposition of the great arteries; L→R = left to right; Memb = membranous; Musc = muscular; OMV = overriding mitral valve; PAB + coarc = pulmonary trunk banding and coarctation repair; subpulm = subpulmonary; vent = ventricular; other abbreviations as in Table I.

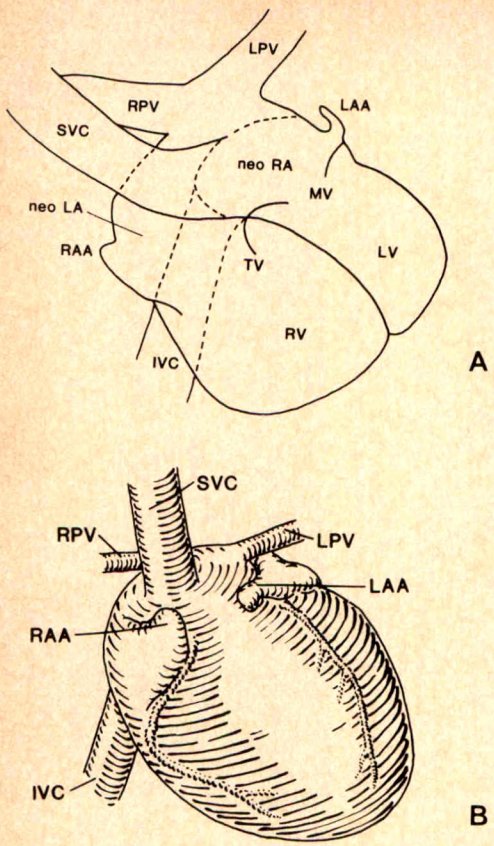

FIGURE 1. A, diagram of atrial and ventricular anatomy after the Senning procedure. The superior vena cava (SVC) and inferior vena cava (IVC) have been moved leftward to drain into the neo-right atrium (neo RA). Around the neo RA "wraps" the hemitorus-shaped neo-left atrium (neo LA), into which the pulmonary veins drain. The morphologic left atrial appendage (LAA) is part of the neo RA and the morphologic right atrial appendage is part of the neo LA. **B,** external view of atrial and ventricular anatomy after the Senning procedure. The great arteries are not depicted so that the relationship between the venous structures may be seen more easily. The neo LA "interlocks" with a second hemitorus, formed by the SVC, IVC, and neo RA. LPV = left pulmonary vein; LV = left ventricle; MV = mitral valve; RPV = right pulmonary vein; RV = right ventricle; TV = tricuspid valve.

d-transposition and ventricular septal defect (6), or double-outlet right ventricle with subpulmonary ventricular septal defect (2) were enrolled in this study. All had been repaired using the Senning procedure and, when necessary, transatrial closure of a ventricular septal defect. In addition, all patients had undergone subxiphoid 2-D echocardiography and cardiac catheterization postoperatively; subxiphoid echocardiographic examinations were performed within 2 weeks of the cardiac catheterization. Cardiac catheterization was performed 2 days to 34 months (median 12 months) after repair.

Eighteen patients had no significant superior vena caval, inferior vena caval, or pulmonary venous obstruction or TR at cardiac catheterization (Group I). Table I summarizes the hemodynamic data of this group. (For the sake of brevity, Group I is referred to as "normal" in the remainder of this report.)

Two patients had isolated superior vena caval obstruction, defined as a pressure gradient between superior vena cava and neo-right atrium of >5 mm Hg at cardiac catheterization (Group II). Three patients had isolated pulmonary venous obstruction, that is, a pressure gradient of >5 mm Hg between either the a wave or the mean of the pulmonary capillary wedge pressure and the simultaneous right ventricular end-diastolic pressure (Group III). Four patients had severe TR demonstrated by right ventricular angiography at cardiac catheterization (Group IV). One of these 4 patients had superior vena caval and mild inferior vena caval obstruction (inferior vena caval–neo-right atrial gradient 4 mm Hg) in addition to severe TR. Finally, 1 patient had a large residual ventricular septal defect with minimal TR (Group V). The hemodynamic data of Groups II through V are summarized in Table II.

Technique: Subxiphoid 2-D echocardiography was performed with a Picker Echoview 80 CI system, using either a 5 mHz short focus (active element diameter 13 mm), 5 mHz long focus (active element diameter 19 mm), or 3.5 mHz long focus (active element diameter 19 mm) crystal.

The systemic and pulmonary venous pathways after the Senning operation resemble 2 interlocking hemi-tori (Fig. 1). Subxiphoid 2-D echocardiography was begun by imaging the heart in the 4-chamber view. Although we centered our transducer and enlarged the image so that only 2 of the 4 chambers were displayed on the screen (namely the 2 atria), this view will still be referred to as the 4-chamber view in the remainder of this report since it represents the same echocardiographic *plane* as a "classic" 4-chamber view. The pulmonary venous atrium (neo-left atrium) appears as a "horseshoe" encircling the systemic venous atrium (neo-right atrium) (Fig. 2). From this view, slight clockwise rotation (10 to 15°) of the transducer displayed the superior vena caval pathway and its junction with the neo-right atrium (Fig. 3). Slight counterclockwise rotation (10 to 15°) from the 4-chamber view displayed the inferior vena caval pathway and its junction with the neo-right atrium (Fig. 4).

The caval pathways and their junction with the neo-right atrium were also easily recognized in a transverse view (Fig. 5). By angling the transducer further to the patient's right from this transverse plane until the caval–neo-right atrial junctions disappeared from view, we were able to image the entire neo-left atrium (Fig. 6).

Measurements: The borders of the caval and pulmonary venous pathways were traced by 2 independent observers on acetate overlays at end-diastole (q wave on the electrocardiogram) for 3 cardiac cycles. From these tracings, the narrowest diameter of the caval and pulmonary venous pathways in each of the 2 views (4-chamber and transverse) were measured. These narrowest diameter measurements are referred to as dimensions in the remainder of this report.

The dimension measurements were normalized to the cube root of body surface area.[11] For each venous pathway, the normalized 4-chamber dimension was multiplied by the normalized transverse dimension to yield a dimension product. In 1 patient only, the inferior vena cava was not imaged in the 4-chamber view. In all other patients, all the venous pathways were imaged in both the 4-chamber and transverse views.

In addition, we qualitatively evaluated systolic expansion of the neo-left atrium as a potential indicator of TR.

Results

The narrowest diameter of the pulmonary venous pathway was uniformly situated at the point where the systemic venous pathway impinges upon the anastomosis between the right pulmonary veins and the old right atrial free wall. This point will be referred to as the isthmus of the neo-left atrium (Fig. 2 and 6).

Group I (normal): The normalized dimensions of the superior vena caval pathway were 10.8 ± 1.2 mm (mean ± standard deviation) (4-chamber view) and 11.2

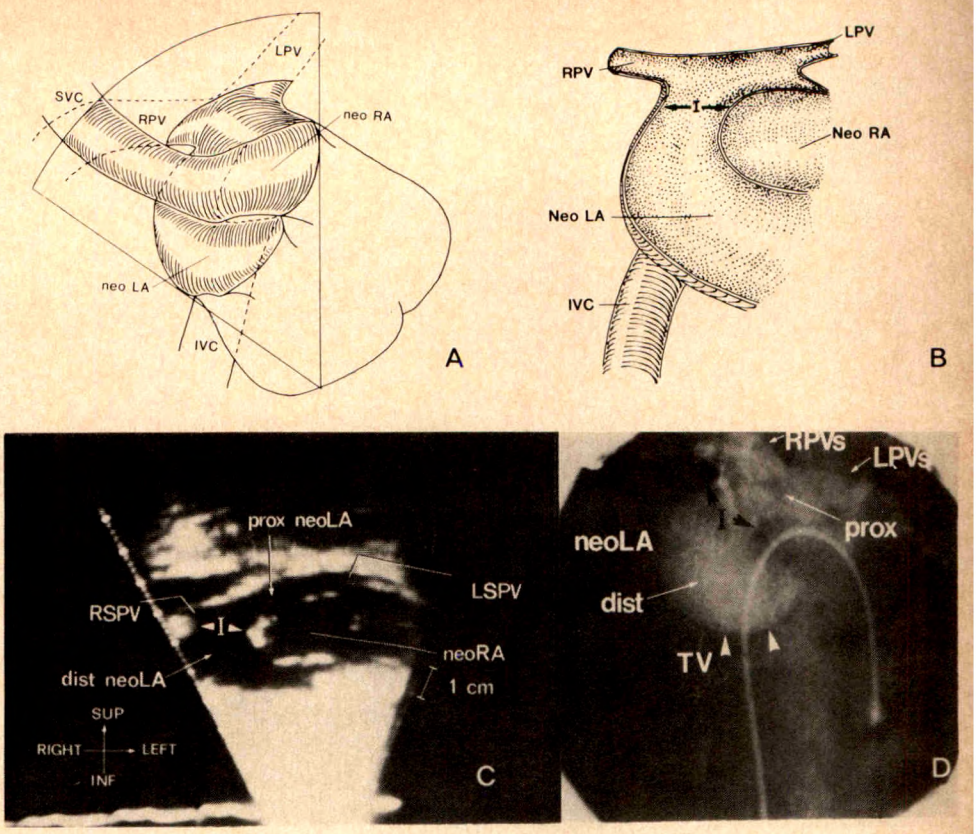

FIGURE 2. A, diagram of the echocardiographic plane used to obtain the subxiphoid 4-chamber view. The sector is directed at only the 2 atria. The shaded structures are on the near side of the sector plane. **B,** diagram of the heart as it would appear if it were "cut open" along the sector plane. The narrowest diameter of the neo-left atrium (neo LA) occurs adjacent to the entrance of the right pulmonary veins. This is termed the isthmus (I) of the neo-left atrium. **C,** 2-D echocardiogram of Patient 9, 4-chamber view. The neo-left atrium consists of a proximal (prox) portion, into which the pulmonary veins drain, and a distal (dist) portion above the tricuspid valve. The isthmus (I) connects the 2 portions of the neo-left atrium. **D,** levophase angiocardiogram of Patient 11, hepatoclavicular view. The catheter, situated in the left ventricular apex, has traversed the inferior vena cava (IVC) and neo-right atrium (neo RA). The hemitoroidal shape of the neo-left atrium, which encircles the neo-right atrium, is easily seen. LSPV = left superior pulmonary vein; RSPV = right superior pulmonary vein. Other abbreviations as in Figure 1.

± 2.3 mm (transverse view). The superior vena caval dimension product ranged from 82 to 194 mm^2. The normalized dimensions of the inferior vena caval pathway were 12.7 ± 3.1 mm (4-chamber view) and 11.7 ± 2.6 mm (transverse view). The inferior vena caval dimension product ranged from 74 to 252 mm.^{2} The normalized dimensions of the isthmus of the neo-left atrium were 18.4 ± 3.4 mm (4-chamber view) and 19.6 ± 3.2 mm (transverse view). The pulmonary venous dimension product ranged between 200 and 516 mm.^{2}

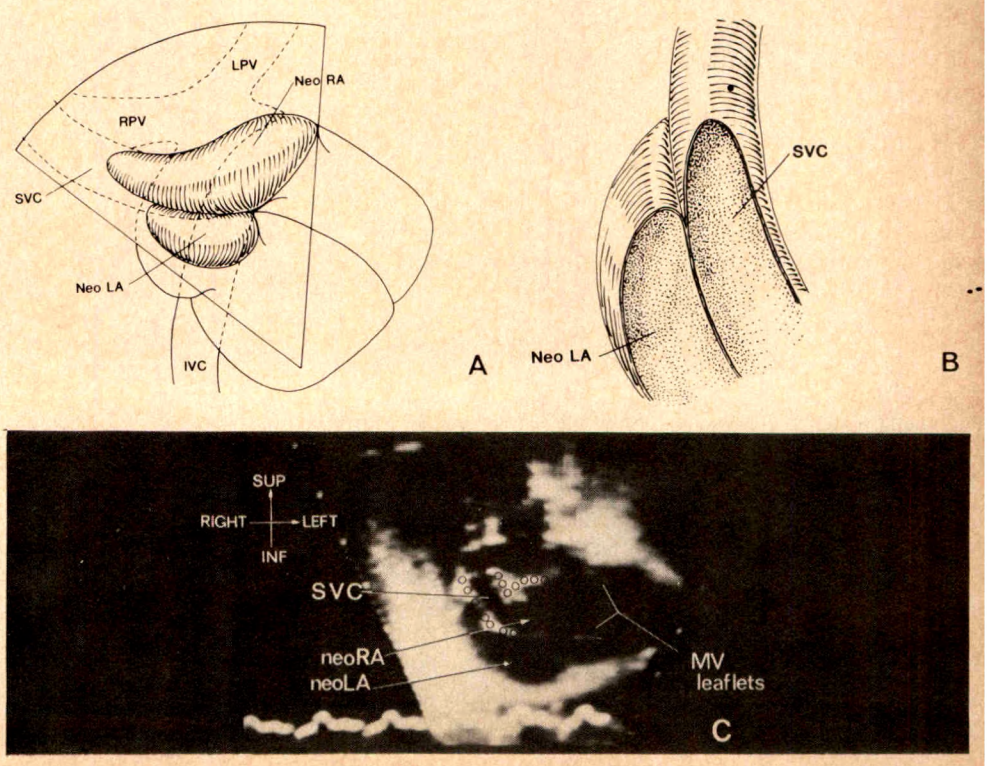

FIGURE 3. A, diagram of the modified 4-chamber echocardiographic plane used to image the superior vena caval–neo-right atrial junction. The shaded structures are on the near side of the sector plane. **B,** diagram of the heart as it would appear if it were "cut open" along the sector plane. **C,** 2-D echocardiogram of the superior vena caval pathway of Patient 18. Abbreviations as in Figure 1.

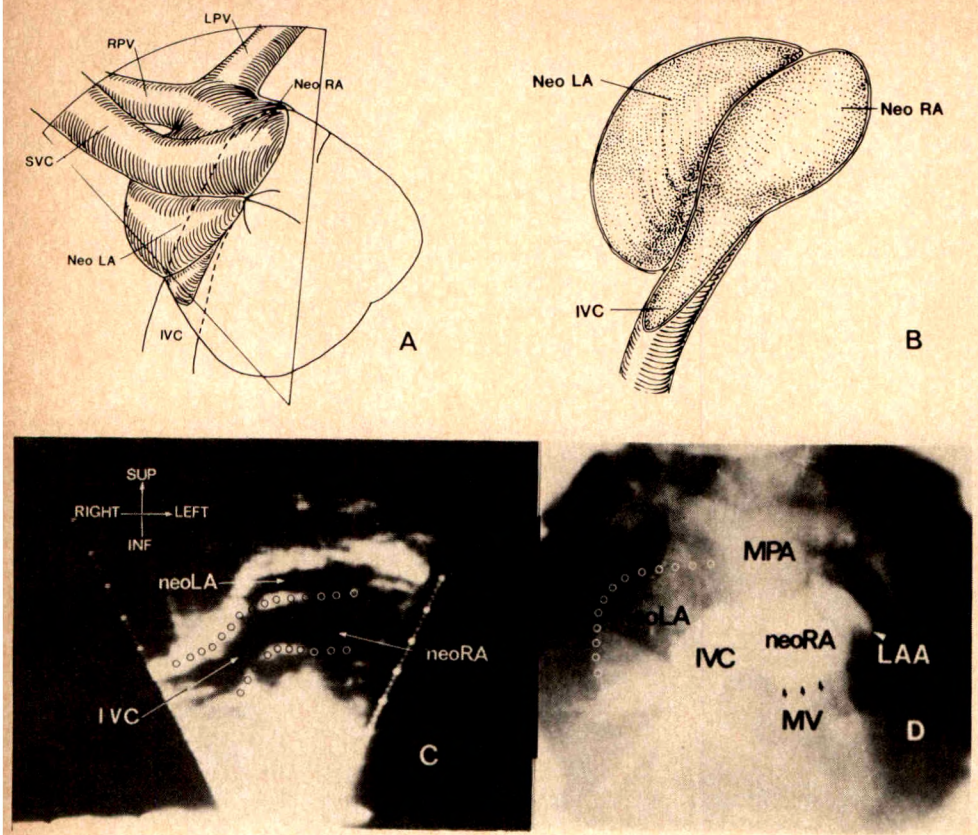

FIGURE 4. A, diagram of the modified 4-chamber echocardiographic plane used to image the inferior vena caval–neo-right atrium junction. The shaded structures are on the near side of the sector plane. **B,** diagram of the heart as it would appear if it were "cut open" along the sector plane. **C,** 2-D echocardiogram of the inferior vena caval pathway of Patient 9. **D,** angiocardiogram of the inferior vena cava and neo-right atrium of Patient 12, hepatoclavicular view. The morphologic left atrial appendage (LAA) is part of the neo-right atrium. The **open circles** outline the border of the neo-left atrium. MPA = main pulmonary artery; other abbreviations as in Figure 1.

Group II (isolated superior vena caval obstruction): The dimension of the superior vena caval pathway in the 4-chamber view for 1 of the 2 Group II patients was clearly outside the normal range; however, the 4-chamber superior vena caval dimension of the other patient was at the lower limits of normal (Fig. 7A). In the transverse view, the superior vena caval pathway dimension for both Group II patients was slightly below normal (Fig. 7B). The superior vena caval dimension product in Group II patients was significantly different

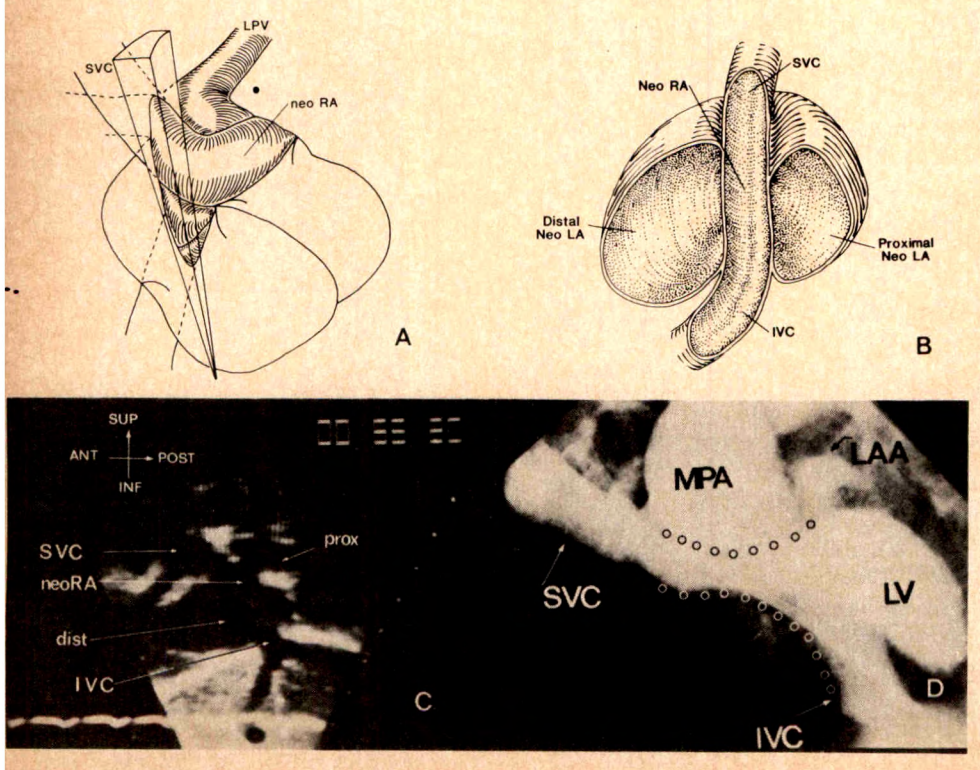

FIGURE 5. A, diagram of the transverse echocardiographic plane of the atria. The shaded structures are on the left side of the sector plane. **B,** diagram of the heart as it would appear if it were "cut open" along the sector plane. **C,** 2-D echocardiogram of Patient 6. The superior vena caval–neo-right atrial and inferior vena caval–neo-right atrial junctions are seen. The distal (dist) portion of the neo-left atrium, immediately above the tricuspid valve, lies anterior to the caval pathways. The proximal (prox) portion of the neo-left atrium, into which the pulmonary veins drain, lies posterior to the caval pathways. **D,** angiocardiogram of the venae cavae of a normal post-Senning patient not included in the study group, long axial oblique view. MPA = main pulmonary artery; other abbreviations as in Figure 1.

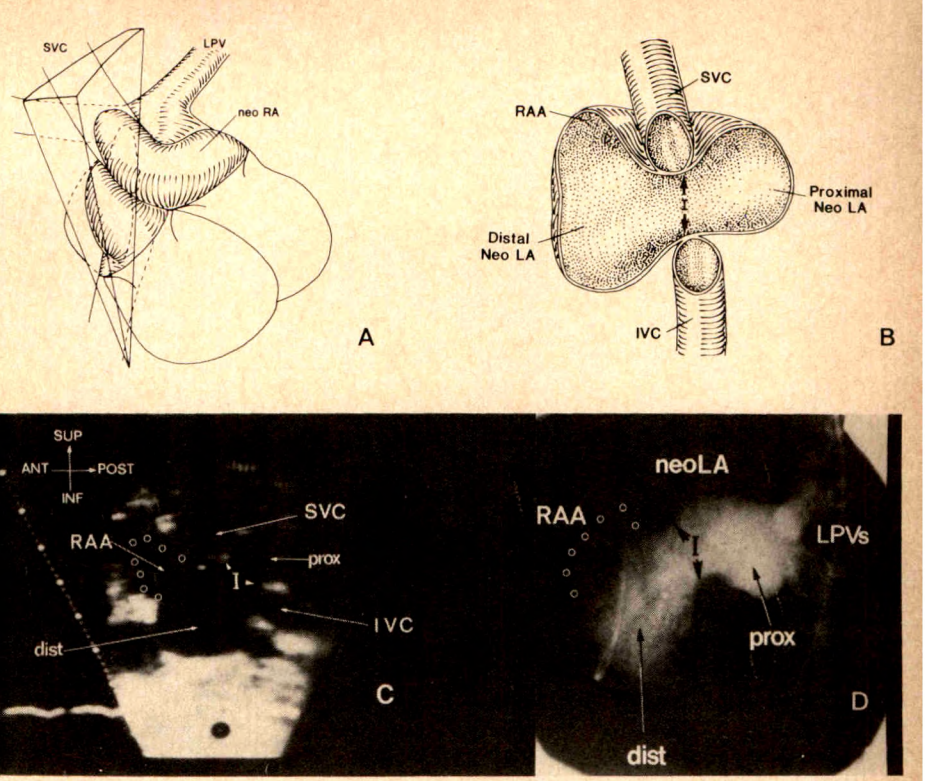

FIGURE 6. A, diagram of the modified transverse echocardiographic plane used to image the neo-left atrium. From the plane diagrammed in Figure 5A, the transducer is aimed slightly to the patient's right until the superior vena caval–neo-right atrial and inferior vena caval–neo-right atrial junctions are no longer visualized. The shaded structures are on the left side of the sector plane. **B,** diagram of the heart as it would appear if it were "cut open" along the sector plane. **C,** 2-D echocardiogram of the neo-left atrium of Patient 6, modified transverse view. The isthmus (I) connects the 2 portions (prox and dist) of the neo-left atrium. The **open circles** outline the border of the morphologic right atrial appendage (RAA), which is part of the distal neo-left atrium. **D,** angiocardiogram of the neo-left atrium of Patient 3, lateral view. The retrograde arterial catheter has been maneuvered from the right ventricular back across the tricuspid valve into the dist neo-left atrium and then into the proximal neo-left atrium, where contrast has been injected. The **open circles** outline the morphologic right atrial appendage (RAA).

($p < 0.05$, Wilcoxon rank-sum test) from Group I patients (Fig. 8A). Figure 9A illustrates the appearance of an obstructed superior vena caval pathway. In both Group II patients, the area of narrowing occurred at the junction of the superior vena cava with the neo-right atrium.

Group III (isolated pulmonary venous obstruction): The dimension of the pulmonary venous pathway in the 4-chamber view of 2 Group III patients was at the lower limits of normal, while the 4-chamber dimension of the other was clearly below normal (Fig. 7E). In the transverse view, the dimension of the pulmonary venous pathway for all 3 Group III patients was just outside the normal range (Fig. 7F). The pulmonary venous pathway dimension product in Group III patients was significantly smaller ($p < 0.01$) than in Group I patients (Fig. 8C). Figure 9, B and C, illustrates the isthmus of the neo-left atrium in a case of pulmonary venous obstruction.

Group IV (severe tricuspid regurgitation): In the 4-chamber view, the dimension of the pulmonary venous pathway was at the upper limits of normal in 2 of 4 Group IV patients and was larger than normal in the other 2 (Fig. 7E). In the transverse view, the pulmonary venous pathway dimension was larger than normal in all 4 Group IV patients (Fig. 7F). The pulmonary venous pathway dimension product in Group IV patients was significantly larger ($p < 0.01$) than Group I patients (Fig. 8C).

The 1 patient with concomitant superior vena caval and mild inferior vena caval obstruction had smaller than normal superior vena caval and inferior vena caval dimension products (Fig. 8, A and B). The 4 patients in Group IV were the only patients in this study with prominent systolic expansion of the neo-left atrium; all qualitatively exhibited enlargement of the entire neo-left atrium, not just the isthmus.

Group V (large residual ventricular septal defect): In the 1 Group V patient, the pulmonary venous pathway dimension was at the upper limits of normal in both the 4-chamber (Fig. 7E) and transverse (Fig. 7F) views. The dimension product was similarly at the upper range of normal (Fig. 8C). This patient did not have prominent systolic expansion of the neo-left atrium.

Interobserver variability: The mean difference in normalized caval dimension measurements between 2 independent observers in each of the 2 views was 1.1 mm, the maximum difference being 2.6 mm. The mean difference in normalized pulmonary venous pathway dimension measurements was 1.5 mm, the maximum difference being 4.5 mm in a patient with severe TR and giant neo-left atrium. Interobserver variability never resulted in dimension product overlap between the groups.

Discussion

The Mustard operation has been evaluated by 2-D echocardiography.[12] Systemic venous obstruction has been detected by 2-D contrast echocardiography,[13] pulsed Doppler echocardiography,[14,15] and radionuclide imaging.[16]

The modified Senning procedure is used by numerous institutions[1–4,6] with operative mortality rates as low as the published mortality rate for the Mustard operation.[17–19] Our study demonstrates the 2-D echocardiographic appearance of the caval and pulmonary venous pathways after the Senning procedure. Furthermore, we have given a range of normal values for the diameter of the caval and pulmonary venous pathways in the 4-chamber and transverse view. The dimension product

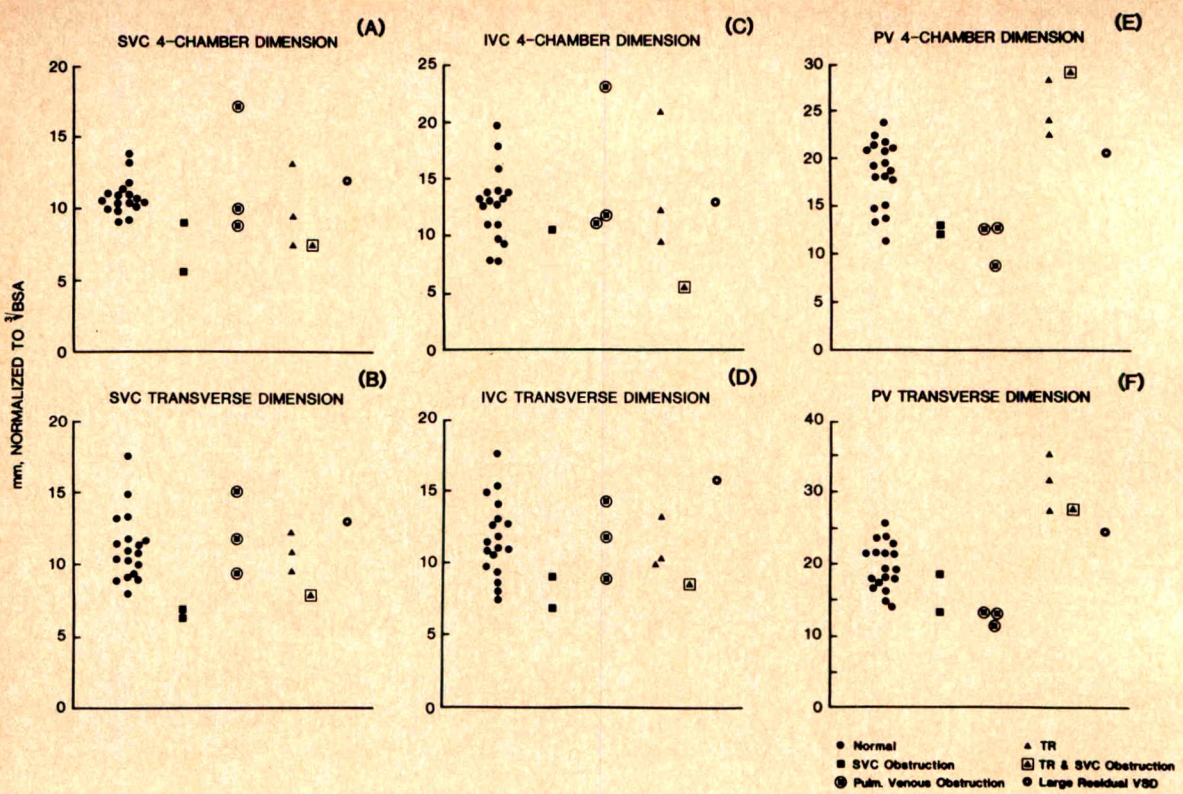

FIGURE 7. Normalized superior vena caval (SVC) dimension measurements in the 4-chamber view (**A**) and in the transverse view (**B**); normalized inferior vena caval (IVC) dimension measurements in the 4-chamber view (**C**) and in the transverse view (**D**); normalized pulmonary venous (PV) pathway dimension measurements in the 4-chamber view (**E**) and in the transverse view (**F**). For 1 of the 2 patients with isolated superior vena caval obstruction, the inferior vena caval 4-chamber dimension was not obtained. BSA = body surface area; TR = tricuspid regurgitation; VSD = ventricular septal defect.

parameter yielded better separation of "normal" post-Senning patients from those with catheterization-proven abnormalities than did either linear dimension alone.

This technique may also be able to detect multiple postoperative abnormalities if all are hemodynamically significant. The patient with combined severe TR and superior vena caval obstruction had both abnormal superior vena caval and pulmonary venous pathway dimension products.

Although the only patients to have the feature of prominent systolic expansion of the neo-left atrium were those with severe TR, we are uncertain if this echocardiographic sign is absolutely reliable in distinguishing TR from residual ventricular septal defect, 2 potential causes of neo-left atrium enlargement. The 1 patient with a large residual ventricular septal defect and minimal TR had a pulmonary venous pathway dimension product at the upper limits of normal but did not have prominent systolic expansion of the neo-left

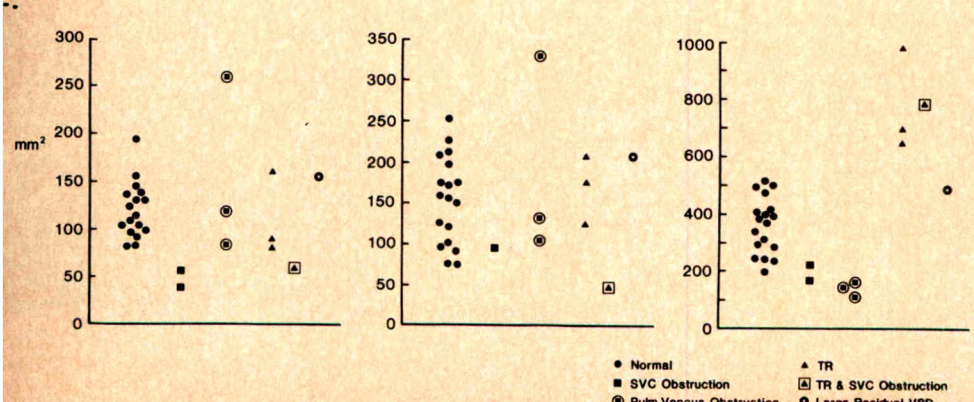

FIGURE 8. A, superior vena caval dimension products. **B,** inferior vena caval dimension products. **C,** pulmonary venous pathway dimension products. For each venous pathway, the dimension product is obtained by multiplying the normalized 4-chamber dimension by the normalized transverse dimension. For 1 of the 2 patients with isolated superior vena caval obstruction, the inferior vena caval dimension product could not be calculated because the inferior vena caval 4-chamber dimension was not obtained. Abbreviations as in Figure 7.

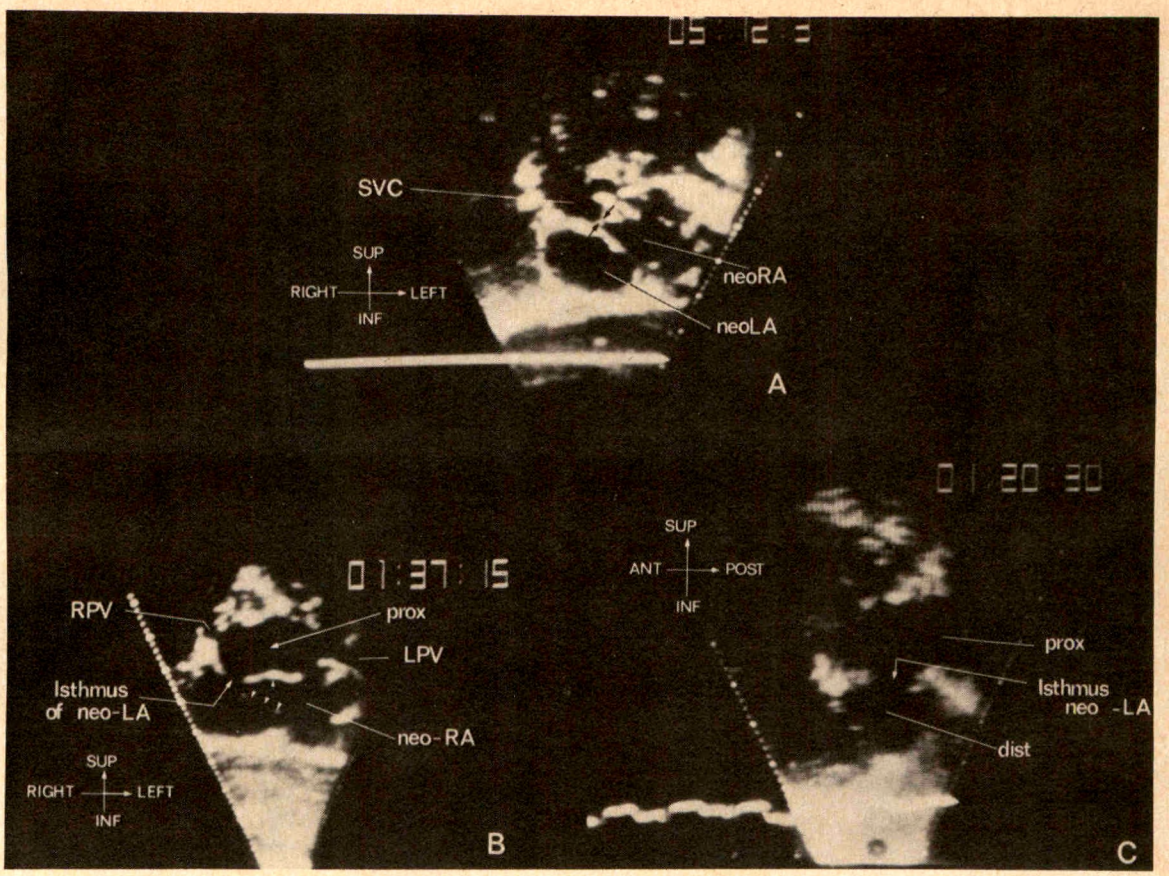

FIGURE 9. A, 2-D echocardiogram of the superior vena caval pathway of Patient 20, modified 4-chamber view. **Black arrowheads** show the narrow superior vena caval–neo-right atrial junction. Compare this with the normal superior vena caval pathway (Fig.3C). **B,** 2-D echocardiogram of Patient 23, 4-chamber view. The **white arrowheads** demonstrate the neo-atrial septum, separating the neo-right atrium from the neo-left atrium. This patient had severe pulmonary venous obstruction at cardiac catheterization. The narrowed isthmus as well as the dilated proximal (prox) portion of the neo-left atrium are visualized. Compare this image with the normal 4-chamber view (Fig. 2C). **C,** 2-D echocardiogram of Patient 23, modified transverse view. Note again the dilated proximal portion of the neo-left atrium and the narrowed isthmus. Compare with the modified transverse view of the neo-left atrium (Fig. 6C). Other abbreviations as in Figure 1.

atrium. More data are needed before we can conclude that systolic expansion of the neo-left atrium specifically indicates TR. We expect that eventually pulsed Doppler echocardiography will help distinguish between TR and residual ventricular septal defect.

Another theoretical limitation to judging TR by assessing neo-left atrium dimensions arises from the fact that patients with d-transposition and large ventricular septal defect usually have large atria before surgery. Presumably, the atria in these patients remain large for some time after the Senning procedure, even in the absence of residual defects. Therefore, interpreting abnormally large neo-left atrium dimensions in the very early postoperative period may be difficult in this group. Among our Group I patients were 3 patients with d-transposition of the great arteries and ventricular septal defect. It is reassuring that all of our Group IV (severe TR) patients had pulmonary venous pathway dimension products significantly higher than these 3 Group I patients. However, the echocardiographic data in these 3 Group I patients were obtained 13 to 17 months after operation rather than in the early postoperative period when the pulmonary venous pathway dimension might have been larger.

In addition, it appears that a large residual ventricular shunt may not always result in an abnormally large pulmonary venous pathway dimension product since our 1 Group V patient was still within the normal range.

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Computer Interpretation of Pediatric Frank Vectorcardiograms in the Evaluation of Congenital Heart Disease

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The evaluation of a new computer program for analysis and interpretation of pediatric Frank vectorcardiograms is reported. The program includes extensive age- and sex-dependent criteria based on tables of limits for numerous vectorcardiographic parameters. In 728 catheterized patients, the diagnostic performance for type A statements was tested against independent and objective evidence obtained from hemodynamic and angiographic data. The overall diagnostic accuracy ranged from 75 to 89% without difference between children <2 years of age and those ≥2 years of age. Sensitivities and specificities of the various diagnoses did not differ much between the 2 age groups. In the younger children, the accuracy of a positive diagnosis of left ventricular hypertrophy, right ventricular hypertrophy, and biventricular hypertrophy was 20, 15, and 32% higher, respectively, than in the older children. The accuracy of the diagnosis "normal" was 28% lower in the younger children. These differences were explained by the higher proportion of pathologic findings in the younger children: 93% versus 74% in the older children.

Given the strict methods of the evaluation, the diagnostic accuracy of this pediatric program was considered clinically satisfactory. Program performance appears to be dependent not on patient age but on prevalence of abnormalities in the population analyzed. Further improvement can be expected by making the criteria more adaptable to the composition of the population.

As compared with computer systems of electrocardiographic analysis in adults, computerized pediatric electrocardiography has specific advantages. First, there are definitely fewer qualified readers of pediatric electrocardiograms, and they are certainly more poorly distributed. Second, the analysis of pediatric electrocardiograms is generally more difficult and requires a more quantitative approach than for adult electrocardiograms. This is due to the wide variation of the normal electrocardiogram from birth to adolescence and to the complexity of abnormalities produced by congenital heart diseases. Computer aid is thus most beneficial in this context, where diagnostic criteria must rely upon extensive use of tables with numerical values (such as for normal and abnormal ranges of amplitude, duration, and angular parameters). However, despite these advantages, there are few computer systems able to process pediatric electrocardiograms. Reports have been published on two 12-lead electrocardiographic analysis programs[1,2] and on 1 vectorcardiographic analysis program.[3] One institution has been routinely processing pediatric vectorcardiograms for some time,[4] and another is collecting a large data bank of pediatric Frank lead electrocardiograms.[5] Screening programs for children have been developed in Germany[6] and in Japan.[7]

Our own computer system of automated electrovectorcardiographic interpretation[8,9] has been extended to enable processing of pediatric Frank lead orthogonal electrocardiograms and vectorcardiograms. Among several advantages, the Frank lead system contains a similar amount of basic information[10] but has 4 times less data to process than the 12-lead electrocardiogram. The normal ranges of Frank electrocardiographic measurements have been extensively studied,[11–16] and their limits are generally narrower than those of 12-lead electrocardiograms.[17] More importantly, the analysis of the spatial vectorcardiogram obtained with the Frank lead system has much diagnostic potential in patients with congenital heart disease as shown by recent correlative studies.[18] This study reports our experience with the current version of the pediatric program rou-

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tinely used for the interpretation of vectorcardiograms in children referred to our institution for the evaluation of congenital heart disease.

Methods

Description of the pediatric program: signal processing and analysis: The input to the pediatric program consists of 10 seconds of simultaneous X, Y, and Z Frank leads sampled at 500/second with 12-bit resolution. The routine which performs the QRS identification and typing is identical to that of the adult program.[8] The rhythm analysis is also basically the same,[19] with some accommodation for pediatric data. Techniques for removal of baseline drift and selective beat averaging allow the obtainment of a noise-free "averaged" P-QRS-T complex on which the rest of the analysis is undertaken. For wave recognition, the pediatric program uses a threshold-crossing method applied to spatial velocity curves to determine various fiducial points. This algorithm was tested on an early set of pediatric records[20] and it has been extensively validated in routinely processing more than 3,000 pediatric records. Since there remains a problem with accurate determination of onset of P wave in records with a very fast heart rate, the automatic interpretation of P-wave contours is being delayed until better algorithms are found. Feature extraction, production of a measurement matrix for selected parameters, and high-resolution vectorcardiographic loop display are the same as for the adult program.[21]

Description of the pediatric program: automatic interpretation of QRS-T contours: The diagnostic criteria are composed of numerous vectorcardiographic parameters, including scalar, planar, and spatial measurements. Both linear and angular values are used, as well as rotation of QRS loop in frontal, sagittal, and transverse planes. This direction of vectorcardiographic loop, as well as maximal and mean spatial QRS and T vectors and loop areas in the various spatial octants, are specific vectorcardiographic parameters used extensively for the diagnosis of ventricular hypertrophies. Most criteria take into account the normal limits of vectorcardiographic measurements according to the patient's age and sex. No clinical data other than age, sex, and information concerning digitalis administration are incorporated into the diagnostic criteria. The normal limits of vectorcardiographic parameters have been obtained by recording and analyzing Frank orthogonal electrocardiograms in 970 children and adolescents aged 2 to 19 years.[22] For children <2 years of age in whom we are still collecting normal records, we currently use normal data from the literature.[5,11,14–15,18] For children ≥2 years of age, we have established the normal limits for 280 vectorcardiographic parameters by using the percentile method[23] with specific statistical tests applied to angular data[24] in 8 different age and sex subgroups.

Because there is always some overlap between normal and abnormal ranges, one cannot rely solely on whether a normal limit is exceeded to decide that a given parameter belongs to the pathologic group. In fact, each diagnostic criterion is composed of several interrelated parameters, some of which have several thresholds. To perform a diagnostic classification, the program follows the deterministic method, that is, Boolean algebra and decision-tree logic.[8] The multiparameter-multithreshold approach allows avoidance of a common pitfall of this conventional deterministic method—the excessive sensitivity of the diagnostic flow to small variations in the value of single parameters.[25] All diagnostic criteria were carefully designed in order to reach the maximum sensitivity and specificity according to the characteristics of our clinical population. These diagnostic criteria were based on current knowledge issued from published data,[18,26–29] from personal studies,[30] and from personal experience in analyzing a huge number of pediatric vectorcardiograms validated by hemodynamic and angiographic studies.

Among the main diagnostic categories so far considered by the program are the following: ectopic sinus or atrial focus; preexcitation pattern (Wolff-Parkinson-White); ventricular conduction defects (both minor and major, such as right bundle branch block with or without right ventricular hypertrophy, left bundle branch block, left anterior fascicular block); left and right ventricular hypertrophies with the degree of severity; combined or biventricular hypertrophy, its degree of severity, and, if appropriate, the type of ventricular dominance; repolarization changes; QRS and T loops within normal limits; some special features, such as abnormal initial vectors suggesting ventricular inversion, pseudoinfarction pattern as in tricuspid atresia, and cardiomyopathies.

Evaluation of the pediatric program in terms of diagnostic accuracy: A formal evaluation of the diagnostic performance of this pediatric program was undertaken along the lines defined at the 10th Bethesda Conference of the American College of Cardiology.[31] Only the type B diagnostic statements, which refer to electrophysiologic events such as conduction disturbances, and the type C diagnostic statements, which are merely electrocardiographic descriptors, such as "nonspecific ST-T changes," were assessed according to the physician's interpretation. All type A diagnostic statements, such as left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH), biventricular hypertrophy (BVH), and absence of cardiovascular abnormalities (NORMAL), which refer to pathophysiologic states and anatomic lesions were validated, not by an electrocardiographer,[32] but exclusively by objective data obtained from hemodynamic and angiographic studies. Most patients underwent a left- and right-sided cardiac catheterization, a few had only a right-sided cardiac catheterization, and biplane cineventriculograms were performed in all. The criteria used to assign a given patient to a diagnostic category, the so-called "clinical diagnosis," are listed in Appendix A. The assignment of each record to a clinical diagnostic category was then made independently, without prior knowledge of the program's interpretation.

A classification matrix was built to compare vectorcardiographic diagnosis with the "true" clinical diagnosis. The results of the diagnostic classification by the program were assessed with respect to multigroup diagnosis, that is, the ability not only to correctly recognize the presence or absence of a given abnormality, but also to avoid making false-positive statements for other abnormalities. Thus, for each diagnostic category, analysis of the classification matrix allowed computation of numbers of true positives, false positives, false negatives, and true negatives and, from these figures, derivation of various indexes of diagnostic performance, such as sensitivity, specificity, accuracy of positive and negative diagnoses, and diagnostic accuracy, following the definitions and rules described in Appendix B.

Results

The study population consisted of a series of 728 young patients referred to our institution for evaluation of congenital heart disease by heart catheterization either as a diagnostic procedure or as preoperative or postoperative check-up. A Frank lead vectorcardiogram was routinely recorded in all these patients, usually on the same day and in no case more than 3 weeks from the invasive study. The clinical characteristics of this population are shown in Tables I and II. Table I lists the age and sex distribution of the patients. Table II shows

TABLE I Age and Sex Distribution of the 728 Catheterized Pediatric Patients

Age	Male	Female
≤1 week	1	1
≤1 month	8	13
≤3 months	22	11
≤6 months	17	23
≤12 months	41	50
≤24 months	27	28
2 to 5 years	162	133
6 to 10 years	64	35
11 to 15 years	37	34
16 to 19 years	10	11
Total	389	339

TABLE II Distribution of the Types of Congenital Heart Disease Among the 728 Catheterized Pediatric Patients

Disease	Number
Right ventricular pressure overload (n = 188)	
Tetralogy of Fallot	71
D-transposition of the great arteries	50
Ventricular septal defect with pulmonic stenosis or pulmonary hypertension	37
Pulmonic stenosis	30
Right ventricular volume overload (n = 77)	
Secundum atrial septal defect	72
Anomalous pulmonary venous return	5
Left ventricular pressure overload (n = 77)	
Aortic stenosis	39
Coarctation of the aorta	38
Left ventricular volume overload (n = 67)	
Patent ductus arteriosus	37
Mitral regurgitation	12
Aortic regurgitation	7
Tricuspid atresia	6
Pulmonic atresia (intact ventricular septum)	5
Combined ventricular overload (n = 173)	
Ventricular septal defect	97
Endocardial cushion defect	39
Multiple defects	18
Single ventricle	10
L-transposition of the great arteries	6
Truncus arteriosus	3
Miscellaneous cardiac anomalies (n = 59)	
Cardiomyopathies or anomalous origin of left coronary artery	17
Ebstein's anomaly	5
Other anomalies	37
No significant cardiovascular disease (n = 87)	

the disease spectrum according to the type of ventricular overloading.

The results of the program's interpretation were first evaluated on a set of 112 records; they were used to modify and optimize diagnostic criteria. This "learning set" was then reanalyzed and a larger "testing set" of 616 records was analyzed. Since there was no significant difference in the results obtained with the 2 sets of records, they were pooled and are presented for the total group of 728 records.

Accuracy of type A diagnostic statements: Since we expected more difficulties in the analysis of records belonging to very young patients, the results were analyzed separately in children <2 years of age and in those ≥2 years of age. The rate of completely correct classifications, that is, correct for diagnostic category and degree of severity or ventricular dominance, was about the same in the 2 age groups: 58% in the younger children and 59% in the older patients. The percentage of satisfactory classifications, that is, allowing for some disagreement about degree of severity or ventricular dominance, was higher in children ≥2 years of age, 73%, versus 67% in the children <2 years of age. In the younger patients, 10 of 16 children (63%) without significant cardiac lesions were correctly classified by the program as normal, whereas 187 of 205 pathologic records (91%) were correctly classified as abnormal. Only 18 patients had moderate to severe LVH (LVH++), of whom 10 (56%) were classified as having either LVH++ or BVH with left ventricular dominance. Sixty-seven of 83 patients (81%) with moderate to severe RVH (RVH++) were classified as having either RVH++ or BVH with right ventricular dominance. The 7 false-negative results misclassified as NORMAL belonged to infants in whom the right ventricular preponderance was considered physiologic. In 82 patients with BVH, 38 (46%) classifications were completely correct, and 50 (61%) were satisfactory, allowing for disagreement about degree of severity or ventricular dominance. In the older children, 61 of 104 records (59%) from normal patients were correctly classified as within normal limits. Twenty-two misclassifications were minor, corresponding to such statements as "possible mild" and "rule out LVH or RVH." Of 293 abnormal records, 258 (88%) were correctly classified in the pathologic group. Thirty-six of 57 cases (63%) with LVH++ as the clinical diagnosis were classified as either LVH++, severe BVH (BVH++), or BVH with left ventricular dominance. Seventeen were misclassified as mild or possible LVH(+) or BVH(+). There were 9 false-positive results for LVH in patients without significant anatomic LVH but whose left maximal spatial voltage was markedly increased. Of 106 patients with RVH++, 94 (89%) were correctly classified. Among 9 false-positive findings of RVH++, there were 4 patients who actually had LVH which produced a rightward posterior displacement of the maximal spatial QRS vector.[26] Thirteen of the 42 patients (31%) with BVH were correctly classified, including degree of severity and type of ventricular dominance. Twenty-six of the classifications of BVH were satisfactory (62%).

Table III shows the various indexes of diagnostic performance.[33] For the total group, sensitivity, specificity, and diagnostic accuracy were, respectively, for LVH: 69, 84, and 78%; for RVH: 84, 74, and 79%; for BVH: 61, 90, and 84%; and for NORMAL: 59, 89, and 84%. There were no striking differences between the 2 age groups. Only the specificity of LVH diagnosis was 10% higher in the younger children (92% versus 81%) and specificity of RVH diagnosis was 20% higher in the older children (77% versus 58%). More important differences between the 2 age groups were noted when results were expressed in terms of accuracy of positive and of negative diagnoses. Indeed, these indexes were influenced by the prevalence of the diagnoses in the population analyzed. So, in the younger children, in whom the prevalence of clinical LVH was higher (52% versus 40%), the accuracy of a positive diagnosis of LVH

TABLE III Diagnostic Performance of Computerized Pediatric Vectorcardiographic Interpretation: Type A Diagnostic Statements

Diagnostic Category	Age	n	Prevalence (%)	Sensitivity (%)	Specificity (%)	Accuracy of Positive Diagnosis (%)	Accuracy of Negative Diagnosis (%)	Diagnostic Accuracy (%)
LVH	<2 years	114	52	71	92	90	75	81
	≥2 years	158	40	67	81	70	79	76
	Total	272	44	69	84	78	77	78
RVH	<2 years	171	77	84	58	87	51	78
	≥2 years	167	42	84	77	73	87	80
	Total	338	55	84	74	79	79	79
BVH	<2 years	82	37	61	88	75	79	78
	≥2 years	42	11	62	90	43	95	87
	Total	124	20	61	90	59	90	84
None	<2 years	16	7	63	91	36	97	89
	≥2 years	104	26	59	88	64	86	80
	Total	120	19	59	89	57	90	84

BVH = biventricular hypertrophy; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy.

was also higher (90% versus 70%). Likewise, in the older children, in whom the prevalence of clinical RVH was low (42% versus 77%), the accuracy of the negative diagnosis of RVH was higher than in the younger children (87% versus 51%). Differences were even more striking for the categories BVH and NORMAL. In the older children, in whom the prevalence of BVH was very low (11%), the accuracy of a negative statement was very high (95%); however, the predictive value of a positive diagnosis of BVH was only 43%, indicating that more than half of the BVH diagnoses were actually false. The predictive value of both a negative and a positive diagnosis of BVH was more satisfactory in the children <2 years of age in whom the prevalence of clinical BVH reached 37%. In the younger children, on the other hand, along with the low prevalence of normal heart (7%), the predictive value of the vectorcardiographic diagnosis of NORMAL was only 36%, whereas the accuracy of the diagnosis of any abnormality reached the value of 97%.

Accuracy of type B and type A + B diagnostic statements: The ability of the program to identify various kinds of ventricular conduction defects was satisfactory, as shown in Table IV. Of particular interest were results corresponding to special features of this program, such as the ability to diagnose RVH in the presence of complete right bundle branch block in 78% of the cases and the ability to draw the reader's attention to specific patterns, indicated in Table IV as "other major abnormalities," such as ectopic sinus or atrial focus, ventricular inversion, and pseudoinfarction as in tricuspid atresia or cardiomyopathy. On the whole, the classification of type B and type A + B statements were completely correct in 88% of the cases, and the accuracy rate for ventricular conduction defects (type B only) was 90%.

Discussion

Our study population consisted of an unselected series of pediatric patients without an attempt to have clear-cut cases. Various kinds of congenital heart disease, sometimes quite complex, were present in 88% of these children and many required surgical treatment. One hundred twenty of the 618 records with a type A diagnostic statement (19%) belonged to patients without significant hemodynamic lesions. In 81% of the records, the clinical diagnosis indicated the presence of LVH, RVH, or BVH, in various degrees, from mild to severe. According to the recommendations of Task Force III at the 10th Bethesda Conference,[31] all type A diagnostic statements were validated using objective data obtained independently of the electrocardiogram

TABLE IV Diagnostic Performance of Computerized Pediatric Vectorcardiographic Interpretation: Type B* and Type A + B† Diagnostic Statements

Diagnostic Category	Cases Called by Physician* and Cases Validated by Catheterization† (n)	Cases Called by Program	
		n	%
Right bundle branch block	79*	78	99
With RVH	55†	43	78
Without RVH	7†	5	
With left anterior hemiblock	14*	13	93
Left anterior hemiblock	79*	73	92
Left bundle branch block	2*	2	. . .
Preexcitation	7*	5	. . .
Minor ventricular conduction defect	35*	35	100
Other major abnormalities	19*,†	19	100

RVH = right ventricular hypertrophy.

as a reference standard, not the physician's opinion.[32] As far as we know, this is the first time a computer program routinely used for the interpretation of pediatric vectorcardiograms was tested against independent and objective evidence for the "true" diagnosis in a large number of cases. A strict methodology also implies that the performance of the program should be assessed with respect to multigroup classification, that is by considering simultaneously all the possible diagnoses and not only 1 category versus another, or normality versus abnormality.

The presentation of the results by means of several indexes of diagnostic performance[33] gives a complete picture of the capabilities of the pediatric program in its present environment. Sensitivity, specificity, and diagnostic accuracy represent intrinsic characteristics of a diagnostic test and these indexes are relatively independent of the composition of the test population. In contrast, the accuracy or predictive value of positive or negative results is a better expression of the diagnostic performance of a test in a given setting, since they are dependent on the prevalence of diagnostic categories in the tested population. These facts were exemplified by the differences of results in the 2 age groups. So, it appeared that in our infants and children <2 years of age, the prevalence of cardiac abnormalities was so high that the vectorcardiographic diagnosis "within normal limits" should always be questioned, since it has many chances to represent a false-negative statement. On the other hand, because of the high prevalence of BVH, the predictive value of this diagnosis was high. Conversely, in children ≥2 years of age, in whom a BVH was much rarer, this diagnosis corresponded to a false-positive result in about 50% of the cases. Thus, it is very unlikely that the same diagnostic criteria would give similar results in drastically different populations.

Given the type of our population with a high proportion of congenital cardiac lesions, and given the strict methods of the evaluation, the diagnostic classification of vectorcardiograms by the current version of the pediatric program gave promising results. As compared with the clinical diagnosis supplied by the hemodynamic and angiographic data, the program performed quite well in the diagnosis of BVH in young children. It is even possible that the method we employed gave an unfavorable picture of the program's behavior. Indeed, in some borderline cases, the clinical classification was forced into a given category because it was impossible to consider many different subsets. Also, cardiac catheterization, as compared with other sources of information such as echocardiography and radionuclide studies, is the "hardest" objective data which can be used to validate a noninvasive diagnostic test, but it is certainly not the only "gold standard."

Finally, it must be recalled that the automatic interpretation provided by the pediatric program has been evaluated in a blind fashion, without any knowledge of the clinical condition of the patient. In actual situations, the pediatrician almost always has some prior information about his patient's condition. He can use the results of the vectorcardiographic analysis in the frame of the total clinical picture. Our system of computer analysis of the pediatric vectorcardiogram must be viewed not as a substitute, but as an aid to the pediatric cardiologist, illustrating the concept of "computer-assisted electrocardiology." The speed of the recording procedure, the precision of the analysis, the production of numerous measurements and of high quality vector loops, and the storage and retrieval capabilities are elements perhaps as important as the automatic interpretation itself.

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Appendix A: Criteria Used for Clinical Diagnosis

Left ventricular hypertrophy (LVH)

Left ventricular pressure overload, for example, aortic stenosis with increased peak systolic gradient (in mm Hg: 25 to 49 = mild, 50 to 79 = moderate, ≥80 = severe).

Left ventricular volume overload with large left-to-right shunts at ventricular or arterial level (pulmonic or systemic flow ratio $\dot{Q}p/\dot{Q}s \geq 1.5$); significant aortic or mitral regurgitation (grade 2 to 4).

Angiographic demonstration of increased left ventricular wall thickness or dilated left ventricular cavity, or both.

Right ventricular hypertrophy (RVH)

Right ventricular pressure overload, for example, pulmonary stenosis with increased peak systolic pressure gradient (in millimeters of mercury: 25 to 49 = mild, 50 to 79 = moderate, ≥80 = severe).

All left-to-right shunts with pulmonary hypertension or increased pulmonary-to-systemic resistance ratio (Rp/Rs: 0.2 to 0.5 = moderate, >0.5 = markedly increased, >0.7 = Eisenmenger complex).

All cyanotic diseases with systolic right ventricular pressure at near systemic levels.

Right ventricular volume overload with large left-to-right shunt at venous or atrial level ($\dot{Q}p/\dot{Q}s \geq 1.5$) and dilated right ventricular cavity.

Angiographic evidence of increased right ventricular wall thickness or dilated right ventricular cavity, or both.

Biventricular hypertrophy (BVH)

Any mixture of criteria of LVH and RVH.

NORMAL

No organic heart disease demonstrated by invasive studies or trivial abnormality without significant hemodynamic consequence, and normal ventricular wall thickness and cavity dimensions.

Appendix B: Definitions and Rules Used for the Assessment of Diagnostic Accuracy of the Pediatric Program

From the classification matrixes one can obtain, for each diagnostic category, the numbers of true-positive, false-positive, false-negative, and true-negative results.

True-positive (TP)

For LVH and RVH: patients with LVH or RVH by clinical diagnosis correctly classified as LVH or RVH, respectively, including same degree of severity plus those classified as BVH (any subcategory), and patients with BVH by clinical diagnosis, classified as LVH or RVH, respectively, or as BVH (any subcategory).

For BVH: only patients with BVH by clinical diagnosis correctly classified as BVH (any subcategory).

For NORMAL: only normal patients by clinical diagnosis correctly classified as normal by the program.

False-positive (FP)

For LVH: non-LVH patients (RVH, NORMAL) by clinical diagnosis misclassified as LVH or BVH, and mild LVH (LVH+) misclassified as marked LVH (LVH++).

For RVH: non-RVH patients (LVH, NORMAL) by clinical diagnosis misclassified as RVH or BVH, and mild RVH (RVH+) misclassified as marked RVH (RVH++).

For BVH: only non-BVH patients (LVH, RVH, NORMAL) by clinical diagnosis misclassified as BVH.

For NORMAL: abnormal patients (LVH, RVH, BVH, including mild cases) by clinical diagnosis misclassified as NORMAL.

False-negative:

For LVH: LVH and BVH patients missed and classified as either RVH or NORMAL, and moderate to severe LVH (LVH++) by clinical diagnosis misclassified as mild, possible LVH (LVH+).

For RVH: RVH and BVH patients missed and classified as either LVH or NORMAL, and moderate to severe RVH (RVH++) by clinical diagnosis misclassified as mild, possible RVH (RVH+).

For BVH: BVH patients missed and classified as either LVH, RVH, or NORMAL.

For NORMAL: NORMAL patients by clinical diagnosis misclassified as abnormal: LVH, RVH, or BVH, including "mild" diagnosis (+).

True-negative (TN)

For LVH, RVH, BVH: non-LVH, non-RVH, non-BVH patients correctly diagnosed.

For NORMAL: all abnormal patients diagnosed as abnormal.

From the numbers of true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) results, one can compute various indexes of diagnostic performance for each diagnostic category:

$$\text{Sensitivity} = [(TP)/(TP + FN)] \times 100.$$

$$\text{Specificity} = [(TN/(TN + FP)] \times 100.$$

$$\text{Accuracy of positive diagnosis} = [(TP)/(TP + FP)] \times 100.$$

$$\text{Accuracy of negative diagnosis} = [(TN)/(TN + FN)] \times 100.$$

$$\text{Diagnostic accuracy} = [(TP + TN)/(TP + TN + FP + FN)] \times 100.$$

Glucose and Insulin Changes in Infants and Children Undergoing Hypothermic Open-Heart Surgery

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Marked hyperglycemia was observed in patients undergoing hypothermic open-heart surgery. To evaluate potential mechanisms responsible for hyperglycemia, paired samples were evaluated for glucose and insulin levels in 3 groups of patients. Group 1 consisted of 8 patients <2 years of age undergoing cardiac surgery requiring total circulatory arrest; Group 2 consisted of 9 patients <2 years of age undergoing open-heart procedures but not requiring total circulatory arrest; Group 3 consisted of 10 patients >2 years of age, none of whom required total circulatory arrest. All 3 groups had striking hyperglycemia during cardiac surgery and in the first few hours after the operation. Despite elevated glucose levels during surgery, insulin levels failed to increase proportionately in response to hyperglycemic stimulus. Subsequently, in a fourth group of 10 patients <2 years of age not undergoing total circulatory arrest, the amount of glucose infused was restricted and they did not have hyperglycemia. In children, osmotic diuresis resulting from hyperglycemia after open-heart surgery may be misinterpreted as an index of satisfactory cardiorenal performance. Accordingly, it is recommended that the diluent added to the pump blood prime solution contain no supplemental glucose; also, intraoperative fluid should consist of a balanced electrolyte solution but no glucose.

In the care of infants and children with congenital heart disease, deep hypothermia with and without total circulatory arrest is used to facilitate open-heart surgery.[1–3] These techniques provide excellent conditions for surgical repair but may subject the patient to profound physiologic alterations.[4–6] One of the most important alterations induced during open-heart hypothermic surgery involves glucose homeostasis. Hyperglycemia and hypoinsulinemia have been documented during cardiac surgery of lower body temperatures in man[7–10] and experimental animals.[11,12] Some workers have found that children have a diminished and delayed insulin response compared with adults,[12] resulting in striking hyperglycemia in these patients.[13,14] The occurrence of hyperglycemia (with glucose levels >700 mg/dl) in 2 patients in our institution led us to evaluate the changes in glucose and insulin levels for infants and children undergoing deep hypothermic cardiovascular surgery. Since exogenous glucose was found to be the major cause of hyperglycemia, restricted infusion of glucose is proposed to prevent this complication in infants and children.

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Methods

Thirty-seven nonconsecutive patients undergoing hypothermic open-heart surgery at the Children's Hospital Medical Center were evaluated. There was no evidence of diabetes mellitus or any other endocrine disorder in any of these patients. These patients were divided into 4 groups. Group 1 consisted of eight patients <2 years of age undergoing procedures requiring total circulatory arrest (TCA); 4 patients had a ventricular septal defect, 1 ostium primum, 2 transposition of the great arteries, and 1 aortic stenosis. Group 2 was composed of 10 patients <2 years of age but not requiring TCA; 8 had ventricular septal defect, and 2 had an atrioventricular canal. Group 3 consisted of 9 patients >2 years of age and not requiring TCA; 1 had a ventricular septal defect, 1 transposition of the great arteries, 1 tricuspid atresia, 2 an atrioventricular canal, 1 pulmonic stenosis, 2 tetralogy of Fallot, and 1 a rhabdomyoma of the right ventricle. After the initial findings in Groups 1 to 3, a fourth group was also

evaluated, composed of 10 patients <2 years not subjected to TCA but receiving restricted glucose output (Group 4).

All patients received premedication with a combination of atropine, ketamine, morphine, pentobarbital, or fentanyl. Deep anesthesia was induced with ketamine and maintained with nitrous oxide, oxygen, d-tubocurarine, pancuronium, morphine, or a combination of these.

All patients were subjected to cardiopulmonary bypass and cooled to a core temperature of 20°C ± 2°C (mean ± SD). The pump perfusion rate was approximately 100 ml/kg/min during hypothermia and 200 ml/kg/min during rewarming. In Groups 1 to 3, the pump priming solution contained blood bank whole blood diluted to a hematocrit of 25 to 30% with 5% dextrose in a lactated Ringer's solution. For Group 4, a nonglucose electrolyte solution (Normosol-R) was substituted for 5% dextrose lactated Ringer's solution in the pump prime. For Groups 1 to 3, routine intravenous fluids contained 5% dextrose. Group 4 received intravenous electrolyte solution without additional glucose. Maintenance potassium was administered during surgery and additional intravenous potassium was given if the serum level decreased to <4.5 mEq/liter. Blood was administered postoperatively to maintain the hematocrit in a range of 30 to 40%.

Group 1 patients were subjected to a period of TCA ranging from 21 to 61 minutes (mean 36). Group 2, 3, and 4 had average intervals of hypothermic myocardial ischemia of 34, 40, and 35 minutes, respectively. Paired blood samples were obtained from an indwelling arterial line for glucose and insulin determinations. Glucose level was measured by a glucose oxidase technique.[15] Mean values are provided for each group ± standard deviation.

Insulin was assayed utilizing a double antibody radioimmunoassay technique as previously described.[15] In our institution, the normal fasting values for glucose range from 50 to 105 mg/dl. Normal values for fasting insulin range from 5 to 10 μU/ml.

Blood samples for Groups 1, 2, and 3 were obtained at the following times: under anesthesia while the patient was receiving intravenous glucose but before the initiation of cardiopulmonary bypass; 5 minutes after the start of bypass; at the beginning of rewarming; at the end of rewarming; and at 1, 2, 3, 4, and 24 hours after perfusion. A record was kept of all intravenous glucose received both in the operating room and in the postoperative period. Group 4 received a restricted glucose input. Neither the pump priming solution nor the routine intraoperative intravenous solution contained any glucose. Blood samples for glucose were obtained 1 hour after perfusion.

Data were analyzed using the Student paired and two-tailed *t* test with $p < 0.05$ considered significant.

Results

The mean body weight of Group 1 was 5.3 ± 1.9 kg and was significantly less ($p < 0.01$) than the Group 2 weight of 8.8 ± 1.9 kg. The mean body weight of Group 3 was 13.1 ± 3.0 kg and was significantly greater than that of Group 1 ($p < 0.01$) and Group 2 ($p < 0.01$).

The pump priming solution of all 3 groups contained a mean of 246 mg/dl of glucose. There was no significant difference in the glucose content of the 3 groups.

The mean rate of intravenous infusion of glucose in the operating room was 11.5 ± 6.4 mg/kg/min in Group 1, which was significantly more than Group 2 (5.8 ± 4.1 mg/kg/min; $p < 0.05$). Group 1 also received significantly more than Group 3 (5.2 ± 2.3; $p < 0.05$). Group 2 did not differ from Group 3. Postoperatively, the rate of glucose infusion in all groups of patients ranged from 1.15 to 1.35 mg/kg/min. There was no significant difference among the groups of patients.

TABLE I Group 1. Glucose and Insulin Changes in Children <2 Years of Age Subjected to Total Circulatory Arrest

	Glucose (mg/dl)		Insulin (μU/ml)	
	Mean	± SD	Mean	± SD
Control	229.9	52.7	8.74	8.25
Prime	267.8	52.5	2.72	2.32
5 Minutes	303.5	50.7	7.96	7.39
End of hypothermia	327.4	68.9	8.80	5.98
End of rewarming	347.6	52.3	16.92	11.40
1 hour	339.5	69.2	7.63	2.84
2 hour	292.6	66.0	10.77	5.30
3 hour	321.9	80.1	16.77	11.16
4 hour	305.0	85.3	18.63	10.67
24 hour	114.5	24.5	9.43	3.57

See text for explanation of sampling.
SD = standard deviation.

In Group 1 (Table I) there was a significant increase in the blood glucose concentration from a mean value of 303 ± 51 mg/dl soon after the onset of cardiopulmonary bypass to 327 ± 69 mg/dl at the time of reinstitution of bypass after TCA. Also, a significant ($p < 0.05$) decrease in the glucose level occurred from the end of the rewarming of the patient (347 ± 51 mg/dl) compared with that observed 2 hours after bypass (293 ± 66 mg/dl) and was significantly different again 3 hours after bypass (322 ± 80 mg/dl). From 4 to 24 hours postoperatively, the glucose level decreased significantly ($p < 0.001$) from 305 ± 85 mg/dl to 114 ± 24 mg/dl.

The insulin levels of Group 1 increase significantly ($p < 0.05$) from 8.8 ± 6.0 μU/ml at the time of reinstitution of perfusion after TCA to 16.9 ± 11.4 μU/ml at the end of rewarming the patient. One hour after rewarming, the insulin level decreased significantly to 7.6 ± 2.84 μU/ml ($p < 0.05$).

In Group 2 (Table II), the mean glucose level at the end of rewarming was 268 ± 41 mg/dl and decreased significantly to 215 ± 57 mg/dl 4 hours postoperatively ($p < 0.05$). The glucose concentration decreased significantly ($p < 0.05$) to 120 ± 24 mg/dl 24 hours postoperatively.

From the end of the hypothermic state during bypass, the insulin level of Group 2 increased significantly ($p < 0.01$) from 5.4 ± 2.4 to 16.8 ± 11.9 μU/ml. When compared with the end of rewarming, insulin levels observed at 1, 2, 3, and 4 hours postoperatively declined significantly ($p < 0.05$) to 8.8 ± 2.8, 8.4 ± 1.3, 8.0 ± 1.7, and 7.9 ± 3.0 μU/ml, respectively.

The glucose levels in Group 3 increased significantly ($p < 0.05$) for a mean of 253 ± 43 mg/dl soon after perfusion was instituted, to 277 ± 50 mg/dl at the end of hypothermia. Subsequently, the glucose level of 268 ± 95 mg/dl at a time of 4 hours postoperatively decreased significantly ($p < 0.01$) to 138 ± 45 mg/dl 24 hours postoperatively.

The insulin levels of Group 3 (Table III) decreased significantly ($p < 0.01$) soon after the onset of perfusion from a mean of 16.0 ± 9.5 μU/ml to 6.1 ± 4.4 μU/ml at

TABLE II Group 2. Glucose and Insulin Changes in Children <2 Years of Age Not Subjected to Total Circulatory Arrest

	Glucose (mg/dl)		Insulin (μU/ml)	
	Mean	± SD	Mean	± SD
Control	162.7	52.3	10.06	7.16
Prime	237.1	60.5	5.94	3.02
5 Minutes	242.9	56.4	8.51	3.76
End of hypothermia	257.2	40.9	5.41	2.42
End of rewarming	267.6	41.0	16.78	11.90
1 hour	284.0	55.0	8.77	2.84
2 hour	289.0	66.7	8.37	1.32
3 hour	247.6	77.2	8.04	1.70
4 hour	215.1	57.3	7.86	2.99
24 hour	120.3	13.6	8.54	1.87

See text for explanation of sampling.
SD = standard deviation.

TABLE III Group 3. Glucose and Insulin Changes in Children >2 Years of Age Not Subjected to Total Circulatory Arrest

	Glucose (mg/dl)		Insulin (μU/ml)	
	Mean	± SD	Mean	± SD
Control	198.7	61.9	9.95	5.66
Prime	234.7	48.3	4.61	2.73
5 Minutes	252.7	42.8	16.04	9.52
End of hypothermia	276.5	50.2	6.10	4.37
End of rewarming	269.8	56.8	48.86	43.40
1 hour	296.0	57.5	12.58	3.55
2 hour	306.3	98.9	14.89	6.26
3 hour	277.1	97.8	14.86	5.80
4 hour	268.0	94.9	15.30	6.29
24 hour	138.4	45.1	21.87	20.97

See text for explanation of sampling
SD = standard deviation.

the end of hypothermia. From the end of the hypothermic state to the end of the rewarming, the mean insulin levels increased significantly ($p < 0.01$) from 6.1 ± 4.4 to 48.9 ± 43 μU/ml. Insulin levels of Group 3 decreased significantly from the end of the rewarming period to 12.6 ± 3.5, 14.9 ± 6.3, 14.9 ± 5.8, and 15.3 ± 6.3 μU/ml at 1, 2, 3, and 4 hours postoperatively ($p < 0.05$), respectively. When other comparisons of glucose and insulin levels were made within Groups 1, 2, and 3, no significant differences were observed using the paired *t* test.

The insulin to glucose ratios for Groups 2 and 3 decreased during the period of cardiopulmonary bypass and deep hypothermia. There was an increase in all 3 groups in response to rewarming, followed by a substantial decrease in the first postoperative hour. Twenty-four hours after surgery, Groups 1 and 2 were found to have normal insulin to glucose ratios but Group 3 had a greater value.

In Group 4, mean weight was 8.7 ± 4.0 kg. The mean serum glucose concentration was 126 ± 28 mg/dl 1 hour after perfusion, compared with values of 339 ± 69 mg/dl for Group 1, 284 ± 55 mg/dl for Group 2, and 296 ± 55 mg/dl for Group 3. The latter 3 groups differ significantly from Group 4 ($p < 0.001$).

Discussion

During the present study, hyperglycemia and hypoinsulinemia were documented in infants and children undergoing hypothermic surgery. Blood glucose levels have been noted previously to be increased during hypothermic cardiac surgery.[4,7,9,14,16–18] This elevation of blood glucose level could result from excessive exogenous glucose infusion, alteration of hormonal levels affecting glucose hemeostasis including decreased or delayed insulin response to hyperglycemia, and decreased peripheral glucose utilization. Our results suggest that a combination of diminished insulin response and excessive glucose infusion accounts for the hyperglycemia.

Hypothermia has been proposed as a primary mechanism for the reduction of insulin secretion by inhibition of the pancreatic secretory process.[11,14,18,19] However, other evidence indicates that insulin secretion is diminished with open-heart surgery even under normothermic conditions.[20] Furthermore, Baum and Porte[10] found that inhibition of insulin secretion could be reversed under conditions of deep hypothermia, suggesting that inhibition of metabolic processes by hypothermia is not the sole factor responsible. In view of the fact that insulin levels decreased 1 hour after surgery when our patients were normothermic, our data suggest that hypothermia is not the primary factor. Hypokalemia and hypocalcemia have also been shown to inhibit insulin release,[4,21,22] but these factors have not been consistently implicated.[4,23,24] The patients in our study were carefully monitored for electrolyte abnormalities both intraoperatively and postoperatively. We found no consistent relationship between levels of potassium or calcium or both and hyperglycemia. This is in agreement with results published by Moffitt et al[25] who showed an elevated glucose level in spite of intraoperative normokalemia and normocalcemia.

Diminished pancreatic blood flow would also cause decreased insulin secretion.[26] The cardiac output is redistributed during deep hypothermia with little decrease in cerebral and coronary flow but a marked decrease in splanchnic, including pancreatic, flow.[27,28] TCA would further compromise pancreatic perfusion and may thus inhibit insulin release. However, Baum and Porte[10] observed no reversal in the inhibition of insulin release with alpha-adrenergic vasodilators and they proposed therefore that blood flow alone was not responsible for this effect. Results from other studies would suggest that diminished pancreatic perfusion is one of the main factors causing hypoinsulinemia.[29,30]

In our study, we noted that the lowest level of insulin occurred during periods of hypothermia and low perfusion rates. The insulin response was improved during rewarming when total body perfusion was maintained by the heart-lung machine. We speculate that cardiac output decreased when patients were taken off bypass and a comcomitant decrease in insulin level was observed. Hyperglycemia was sustained by exogenous intravenous glucose infusion.

When the glucose concentration of the heart-lung machine before the onset of bypass is similar to that of the patient and is also similar at the time perfusion is

discontinued, then the pump prime solution may make little contribution to the glucose homeostasis of the patient. This assumes that the volume of fluid in the heart-lung machine initially and at termination of bypass are equal, which may not always be true. However, blood discarded by suction intraoperatively and postoperatively may compensate for differences. The glucose infused intravenously, however, is more significant.

From our observations, excessive glucose is administered intravenously in the operating room. The smaller the child, the proportionately greater is the amount of excessive glucose infused. Since the insulin level was depressed during these operative procedures, it would seem prudent to restrict glucose input in the operating room. Similarly, Freidenberg et al[31] recommended caution in the use of glucose-containing solution during the postoperative management of patients undergoing cranial surgery. These investigators reported severe hyperglycemia with coma in patients who had diabetes insipidus while receiving dexamethasone, an antagonist of insulin action. Excessive fluid loss by way of polyuria was replaced with glucose-containing solutions; this compounded fluid loss by inducing an osmotic diuresis superimposed on the diabetes insipidus. The problem was resolved by avoiding glucose solutions in combination with appropriate use of antidiuretic hormone. Hyperglycemia of the magnitude observed in our patients in combination with the low insulin levels indicates that glucose was not being metabolized. Such hyperglycemia would also cause an osmotic diuresis. Since urine output is used as one measure of assessing the adequacy of cardiorenal performance, osmotic diuresis may be misinterpreted as a salutary response. Thus, prevention of hyperglycemia is of value in patient care. Furthermore, we have documented no disadvantage to restriction of glucose input in the operating room. Postoperatively, we have found no need to change the glucose infusion rate from that usually employed. When exogenous glucose was eliminated from the intravenous electrolyte fluids, hyperglycemia did not occur (Group 4).

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Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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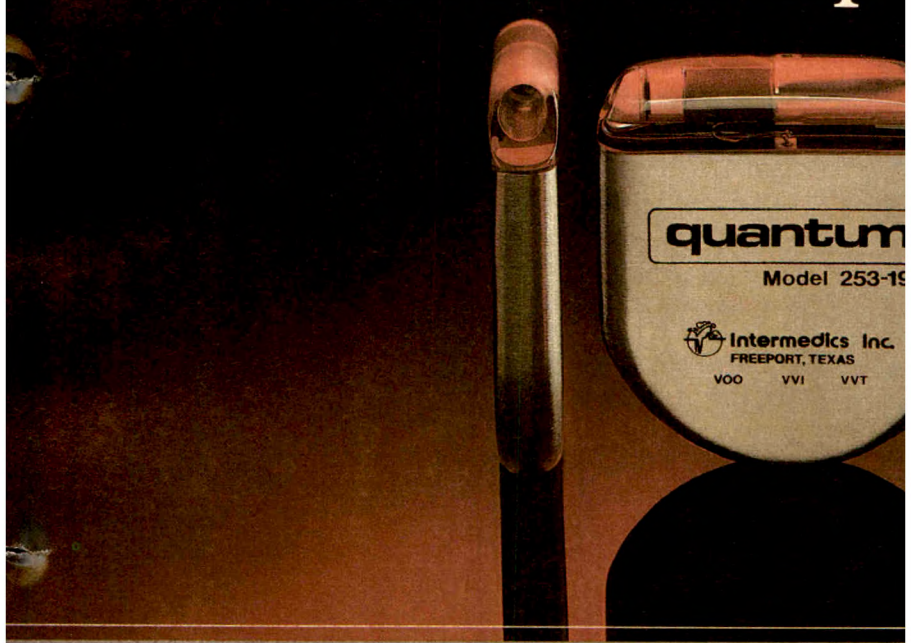

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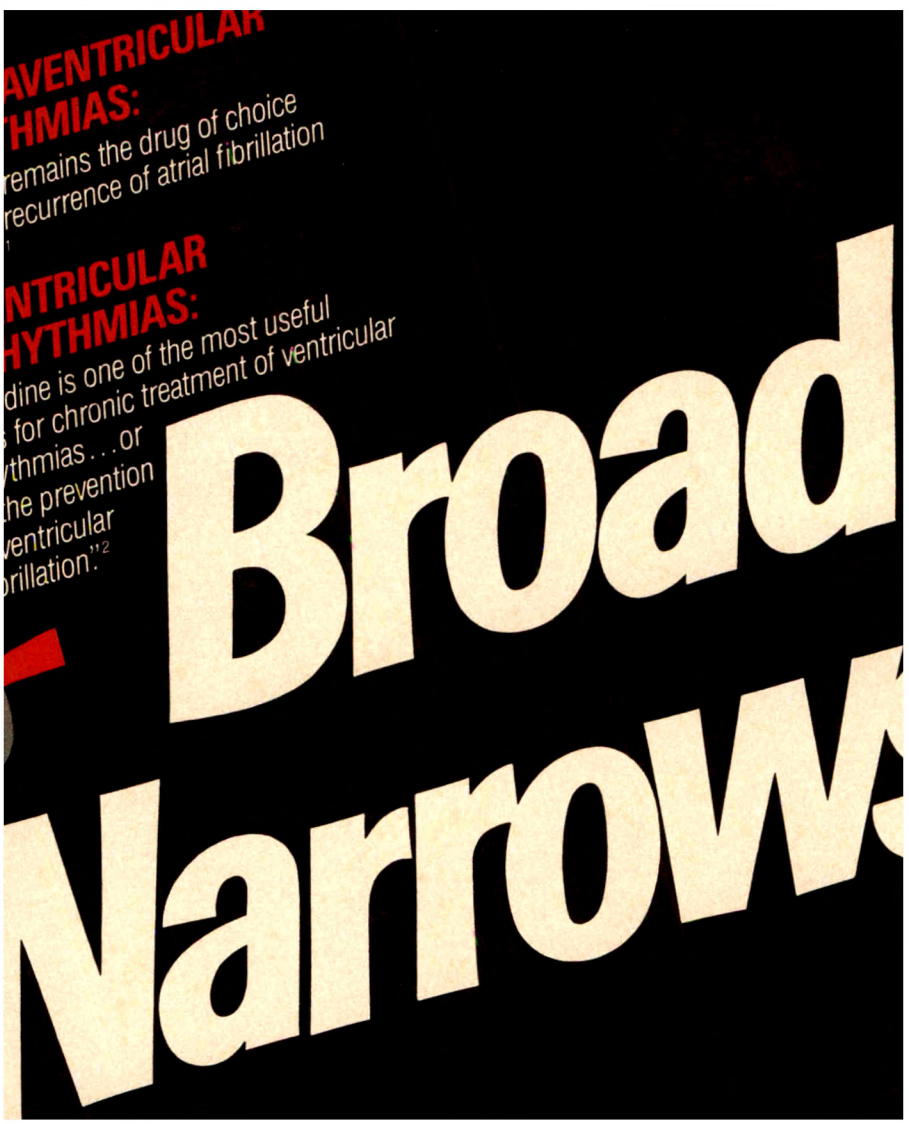
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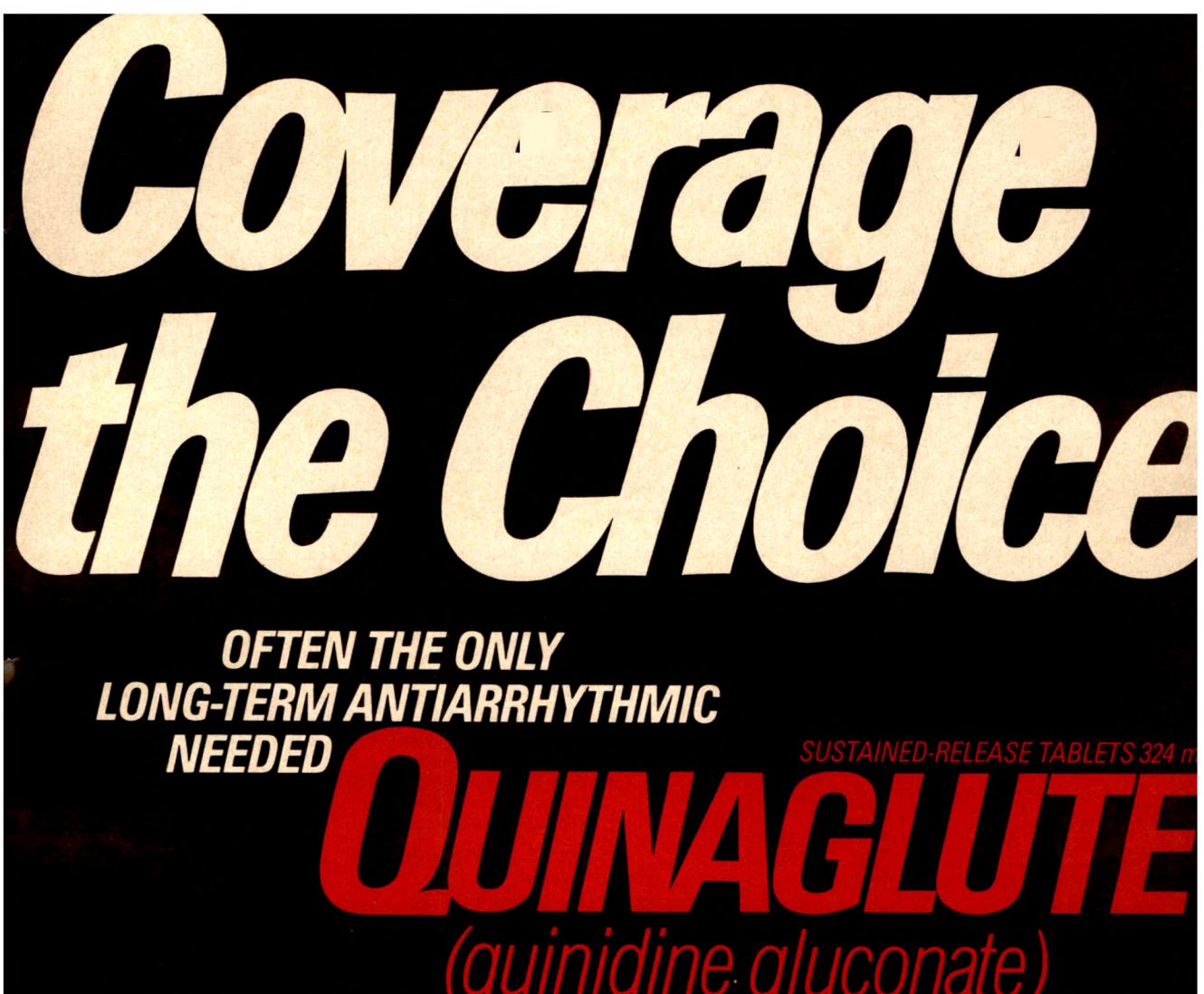
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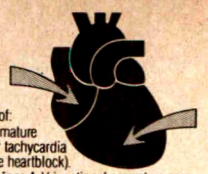

INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. 2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered. 3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring. 4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals. 5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity. 7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal. 8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.
Drug Interactions:

Drug	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
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Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC
Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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Cardiac Amyloidosis Causing Cardiac Dysfunction: Analysis of 54 Necropsy Patients

WILLIAM C. ROBERTS, MD and BRUCE F. WALLER, MD

Clinical and morphologic findings are described in 54 necropsy patients (32 men [59%]) aged 21 to 97 years (mean 64) with cardiac amyloid deposits extensive enough to cause fatal cardiac dysfunction. Chronic congestive heart failure (CHF) was present in 46 (85%). The duration of CHF, known in 39 patients, ranged from 1 to 108 months (mean 18) and lasted ≤12 months in 25 patients (64%). All 8 patients without CHF died suddenly and unexpectedly. Systemic arterial pressures were recorded in the last 3 months of life in 43 patients: the peak indirect systolic pressure was ≤130 mm Hg and the diastolic pressure <90 mm Hg in all. Electrocardiograms, recorded in the last 6 months of life in 40 patients, were abnormal in each: low voltage in 35 (63%); "myocardial infarction pattern" in 33 (83%); abnormal QRS axis in 29 (73%); arrhythmias in 29 (73%); first, second, or third degree heart block in 28 (45%); and complete bundle branch block in 7 (18%). In 30 patients, the QRS amplitude in all 12 leads was measured: in the 15 men it ranged from 60 to 197 mm (mean 99) (10 mm = 1 mV) and in the 15 women from 58 to 199 mm (mean 109). Diagnosis of amyloidosis was established by biopsy of noncardiac organs or tissues during life in only 18 (33%) patients. During life the condition simulated hypertrophic cardiomyopathy in 5 patients, constrictive pericardial disease in 3, and coronary heart disease (because of angina pectoris) in 4.

At necropsy, the hearts ranged in weight from 300 to 900 g (mean 554), and all but 1 had a "rubbery," noncompliant consistency. In addition to their presence in myocardial interstitium (53 patients) and in intramural coronary arteries (54 patients), amyloid deposits were present grossly in mural endocardium in all 54 patients and in valvular endocardium in 46 (85%). The cardiac ventricles were not dilated in 43 patients (80%), but both atria were dilated in all 54 patients. Intracardiac thrombi were present in 14 patients (26%). Cardiac amyloidosis must be considered in any elderly patient with chronic CHF unassociated with chest pain when blood pressure is normal and the electrocardiogram discloses low voltage and a pattern of "healed myocardial infarction."

In 1970, clinical and necropsy findings in 15 patients with cardiac dysfunction secondary to cardiac amyloidosis were reported from this laboratory.[1] During the past 13 years we have studied at necropsy an additional 39 patients with fatal cardiac amyloidosis. This report summarizes clinical and morphologic findings in these 54 patients with cardiac amyloid deposits extensive enough to cause cardiac dysfunction, with particular emphasis on electrocardiographic observations.

Patients Studied and Findings

Clinical findings: The 54 patients ranged in age at death from 21 to 97 years (mean 64). The 32 men (59%) ranged in age from 32 to 97 years (mean 65) and the 22 women (41%) from 21 to 93 years (mean 62) (Fig. 1). Thirty-eight (70%) were white and 16 (30%) were black. Of the 54 patients, 46 (85%) had clinical evidence of congestive heart failure (CHF) at some time. The duration of CHF was discernible in 39 of the 46 patients and ranged from 1 to 108 months (mean 18): for ≤12 months in 25 patients (64%), from >12 to 24 months in 6 patients (15%), from >24 to 36 months in 3 patients (8%), and from 60 to 108 months (mean 82) in 5 patients (13%). The duration of CHF in 18 women ranged from 1 to 72 months (mean 18) and in 25 men from 2 to 108 months (mean 22). Each of the 8 patients (15%) without clinical evidence of CHF died suddenly and unexpectedly: in 3 sudden death was the first evidence of amyloidosis, 2 had familial amyloidosis, 2 had multiple myeloma, and 1 clinically had presumed alcoholic cirrhosis (which at necropsy actually was massive hepatic amyloid infiltration). The 8 patients dying suddenly without ever having clinical evidence of CHF ranged in age from 21 to 88 years (mean 56) and the 46 patients with CHF from 32 to 97 years (mean 65). Chest pain was present at some time during amyloid illness in 8 patients (15%), 4 of whom were considered to have angina pectoris.[2,3] Of the 4 patients (aged

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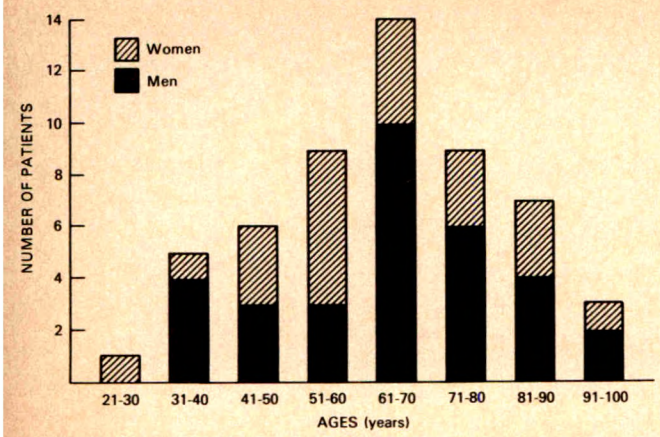

FIGURE 1. Age and sex distribution in the 54 necropsy patients with cardiac amyloidosis extensive enough to cause cardiac dysfunction.

67 to 89 years [mean 80]) with angina, 2 at necropsy had 1 or more of the 4 major (right, left main, left anterior descending, and left circumflex) epicardial coronary arteries narrowed 76 to 100% in cross-sectional area by atherosclerotic plaques.

Seven patients (13%) had histories of illnesses considered compatible with acute myocardial infarction that healed, but electrocardiographic and enzymatic documentation of myocardial necrosis at the time was unavailable. Grossly visible left ventricular scars, however, were absent at necropsy in all 7 patients, indicating that the histories of acute myocardial infarction in them were fallacious.

Four patients (7%) had 1 or more episodes of syncope. One patient was among the 4 with familial amyloidosis with peripheral neuropathy and postural hypotension. The mechanism of the syncope in the other 3 patients was not determined.

Systemic arterial pressure recordings during the last 3 months of life were available in 43 (80%) of the 54 patients. Although 24 (44%) of the 54 patients had a history of "hypertension," in none of the 43 patients (including the 24) with indirect blood pressure recordings available during the last 3 months of life was the systolic pressure >130 mm Hg or the diastolic pressure >90 mm Hg. The range of systolic arterial pressures during the last 3 months of life was 80 to 130 mm Hg (average 102) and of diastolic pressures 40 to 90 mm Hg (average 66).

TABLE I Cardiac Amyloid Causing Cardiac Dysfunction: Electrocardiographic Observations in 40 Patients*

Abnormality [No. (%)]	No. of Patients (%)
1. Low voltage (QRS ≤15 mm in I + II + III)	25 (63)
2. Myocardial infarct pattern	33 (83)
Anterior = 26 (79)	
Posterior = 2 (6)	
Both = 5 (15)	
3. Abnormal QRS axis	29 (73)
Right (+111 to +210°) = 6 (21)	
Left (−30 to −90°) = 23 (79)	
4. Arrhythmias	29 (73)
Atrial fibrillation = 9 (31)	
Atrial or junctional tachycardia = 10 (34)	
Ventricular premature complexes = 21 (72)	
5. Heart block	18 (45)
P-R interval >0.20 = 9 (50)	
2° AV block = 4 (22)	
3° AV block = 5 (28)	
6. Complete bundle branch block (QRS ≥0.12)	7 (18)
Right = 5	
Left = 2	

AV = atrioventricular.
* Numbers in parentheses represent percentages.

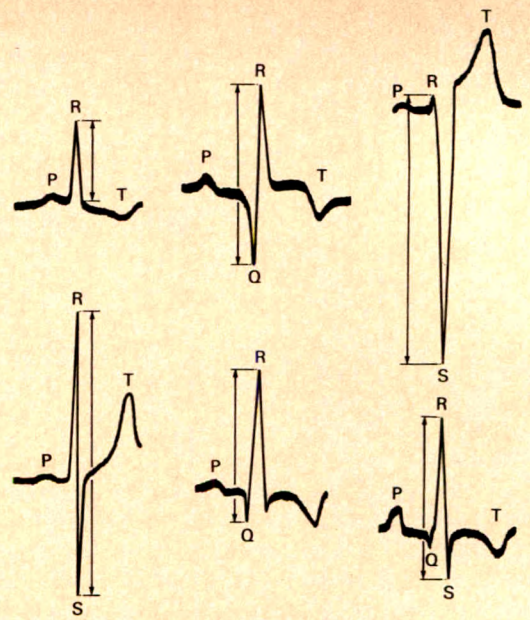

FIGURE 2. Various QRS complexes showing how each was measured.

The cardiac silhouette was enlarged on chest roentgenogram during the last few months of life in 39 (72%) of 54 patients. In several patients, however, earlier radiographs had shown the cardiac silhouette to be of normal size.

Adequate information on precordial examinations during the last few months of life was available in 44 of the 54 patients, 36 (82%) of whom had precordial murmurs. They were of a blowing type and consistent with mitral or tricuspid regurgitation, or both, in 35 (97%): grade 1 to 2/6 in 26, grade 3/6 in 7, and grade 4/6 in 2 patients. In addition, 1 patient had a murmur typical of valvular aortic stenosis (grade 3/6), which was confirmed to be present and was the type typically observed in the elderly.[4] At least 22 patients had third heart sounds (S_3) and at least 8 patients had fourth heart sounds (S_4).

Reports of 1 or more electrocardiograms recorded in the last 6 months of life were available in 40 patients, and all were abnormal (Table I). Of the 40 patients, electrocardiograms, recorded 0 to 160 days (mean 41) before death, were available for reexamination in 30 (Table II). In each of these 30 patients (15 women and 15 men), the QRS amplitude in all 12 leads was measured (Fig. 2). The total 12-lead QRS amplitude in the 15 men (mean age 52 years) ranged from 60 to 197 mm (mean 99) (10 mm = 1 mV) and in the 15 women (mean age 65 years) from 58 to 199 mm (mean 109). The heart weights in the 15 men ranged from 410 to 750 g (mean 570), and in the 15 women from 370 to 900 g (mean (494) ($p < 0.01$). Some electrocardiograms are illustrated in Figures 3 to 6.

Information regarding digitalis therapy was available in 40 patients, and 31 of them received this drug. At least 12 (39%) of the 31 patients developed physical or electrical signs, or both, considered typical of digitalis toxicity.

M-mode echocardiograms were performed in the last few months of life in 11 patients. The findings are summarized in Table III and illustrated in Figures 6 and 7.

Cardiac catheterization was performed in the last few months of life in 10 patients (19%), and the findings are summarized in Table IV.

Of the 54 patients, the amyloidosis was primary in 42 (78%), associated with multiple myeloma in 7 (13%), and familial in 5 (9%). None of the 54 patients had "secondary" amyloidosis.

Diagnosis of amyloidosis was established by biopsy of noncardiac organs or tissues during life in 18 patients (33%), including 5 of the 8 patients without and in 13 (28%) of the 46 patients with chronic CHF. Of the 21 patients having undergone biopsy of noncardiac organs or tissues, findings in 18 were positive for amyloid: rectum, 6 of 6; gingiva, 3 of 4; liver, 3 of 3; tongue, 2 of 3; kidney, 1 of 2; and each of prostate gland, thyroid gland, and lymph node, 1 of 1. In addition, endomyocardial biopsy of the right ventricular aspect of the ventricular septum was performed in 1 patient, but amyloid was not observed on histologic examination.

Of the 46 patients with chronic CHF, biopsy of a noncardiac organ or tissue was performed in 10 and all findings were positive for amyloid. In addition to these 10 patients, amyloidosis was considered the most likely cause of chronic CHF in 9 other patients. The cause of chronic CHF was never established during life in the remaining 27 patients (59%). Of the 11 patients having undergone M-mode echocardiography, the maximal thickness of the ventricular septum was greater than that of the left ventricular free wall in 5, and as a consequence hypertrophic cardiomyopathy was the suspected diagnosis clinically in each of them (Fig. 8 and 9). One of these 5 patients also had undergone cardiac catheterization, and hypertrophic cardiomyopathy continued to be the most likely clinical cardiac diagnosis after that procedure. Inability to differentiate clinically between constrictive pericardial disease and restrictive cardiomyopathy led to thoracotomy in 3 patients. At operation, all 3 had normal visceral and parietal pericardia and normal amounts of pericardial fluid. Each of these 3 patients died within 5 days of thoracotomy.

Eight patients had transient episodes of chest pain. In 4 the pain was consistent with angina pectoris, and a diagnosis of coronary heart disease was made in each. At necropsy, however, only 2 of the 4 patients had significant narrowing of an epicardial coronary artery by atherosclerotic plaque. Of the 4 patients with chest pain not consistent with myocardial ischemia, 1 had significant narrowing of 1 or more epicardial coronary arteries by atherosclerotic plaques. One of the latter 4 patients was 1 of the 3 with clinical pericardial constriction syndrome. The cause of chest pain in the other 2 was unclear. All 8 patients with chest pain had chronic CHF, and 2 had a history of acute myocardial infarction in the remote past. All 8 patients had luminal narrowing of many intramural coronary arteries by amyloid deposits.

Morphologic findings: The hearts in all 54 patients were examined initially by 1 of us (WCR), and 40 were reexamined together by both of us. Heart weights, available in 50 of the 54 patients, ranged from 300 to 900 g (mean 554). Of the 22 women, heart weights, available in 19, ranged from 300 to 900 g (mean 484) and 17 (89%) of the 19 weighed >350 g (a weight considered the upper limit of normal in adult women). Of the 32 men, heart weights (available in 31) ranged from 410 to 900 g (mean 596) and all 31 weighed >400 g (a weight considered the upper limit of normal in men).

TABLE II Electrocardiographic QRS Voltage (mm) in Each of 12 Leads in 15 Men and 15 Women With Cardiac Amyloidosis Causing Fatal Cardiac Dysfunction

Case	Necropsy Number	Age (yr) at Death	Interval (Days) ECG to Death	Leads I	II	III	R	L	F	V_1	V_2	V_3	V_4	V_5	V_6	Total QRS 12-Lead	Heart Weight (g)
Men																	
1	A63-125	32	88	6	10	6	8	4	7	11	23	16	14	11	9	125	700
2	Vt. MCV A75-174	35	56	4	4	3	4	3	4	5	9	9	11	13	8	77	750
3	A65-159	38	10	2	4	6	2	5	6	5	19	11	6	9	7	82	410
4	A70-254	38	2	2	2	5	1	3	3	4	18	16	16	9	5	84	600
5	A79-25	45	2	5	4	8	2	6	6	12	27	21	22	30	15	158	780
6	A81-6	46	13	5	5	5	4	4	3	2	10	17	19	19	13	106	545
7	NNMC 80A-15	49	107	6	3	4	3	6	3	14	20	15	12	9	4	99	850
8	A60-19	54	0	4	4	1	4	3	3	10	10	3	10	8	5	65	550
9	A56-81	55	23	2	3	2	2	1	3	5	9	11	11	7	4	60	480
10	A61-190	55	2	2	4	5	3	4	5	3	15	14	12	12	6	85	535
11	GT 74A-259	62	9	2	3	3	2	2	3	1	6	23	21	11	2	79	470
12	A65-232	65	103	7	20	12	11	3	15	8	15	24	32	27	23	197	560
13	A69-187	68	5	5	5	7	3	6	6	13	16	11	9	8	6	95	550
14	A67-241	68	35	9	5	6	7	7	3	11	7	13	15	12	6	101	420
15	A66-151	69	59	4	3	5	3	5	4	7	10	11	8	5	4	69	450
Mean		52	34	4.3	5.3	5.2	3.9	4.1	4.9	7.4	14.3	14.3	14.5	12.7	7.8	99	570
Women																	
1	A65-25	21	58	5	5	5	5	5	3	11	28	30	16	10	12	135	530
2	A68-23	48	50	4	3	3	3	3	3	5	7	9	8	9	8	65	450
3	GT 80A-262	50	91	4	3	3	2	3	3	11	24	20	18	11	14	116	460
4	A68-277	53	15	3	2	3	1	3	3	6	10	10	10	4	3	58	370
5	HU A77-19	54	51	5	2	8	2	7	6	7	15	15	4	7	6	84	420
6	Wil., D. WMC A79-24	55	8	1	8	9	4	5	9	14	21	17	9	9	5	110	430
7	SH A81-47	61	0	2	6	6	5	3	6	6	19	21	16	9	8	107	385
8	GT 71A-67	67	76	8	8	8	7	6	7	7	19	18	17	14	8	127	650
9	GT 81A-90	70	42	3	4	2	3	1	3	3	11	14	9	8	7	68	485
10	GT 71A-435	72	70	5	14	12	9	6	12	3	4	12	24	12	8	121	480
11	SH A79-76	75	30	7	10	7	6	12	5	16	18	17	17	15	15	145	510
12	GT 79A-127	78	49	3	5	4	4	2	3	4	9	16	17	21	9	97	520
13	WHC A82-120	82	6	5	8	12	4	7	10	8	18	34	41	25	27	199	900
14	GT 79A-195	89	160	3	5	1	4	2	3	3	9	14	18	20	9	91	440
15	Sibley A80-99	93	3	10	6	12	5	10	10	9	10	11	14	14	6	117	380
Mean		65	47	4.5	5.9	6.3	4.3	5.0	5.7	7.5	14.8	17.2	15.8	12.5	9.7	109	494
Total (mean)		58	41	4.4	5.6	5.8	4.1	4.6	5.3	7.5	14.5	15.8	15.2	12.6	8.7	104	532

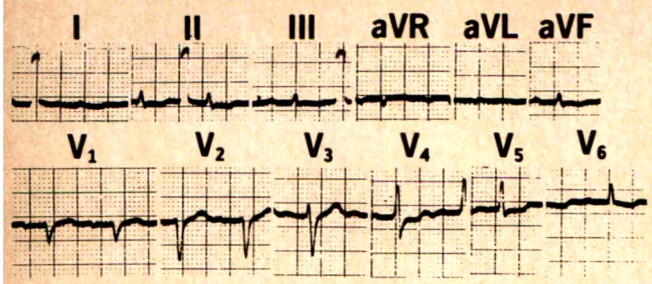

FIGURE 3. Electrocardiogram in a 55-year-old man (A56-81) recorded 23 days before death. The patient never had congestive heart failure. The heart weighed 480 g. The total 12-lead QRS voltage is only 60 mm. R waves are absent in leads V_1 and V_2 and small in V_3.

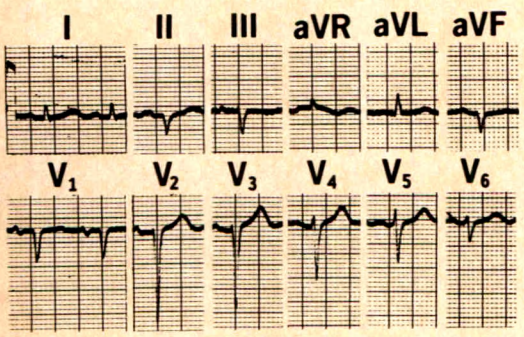

FIGURE 4. Electrocardiogram in a 55-year-old man (A61-190) recorded 2 days before death. The heart weighed 535 g and the total 12-lead QRS voltage is 85 mm. The voltage is decreased. The axis is leftward, Q waves are present in leads II, III, and aVF, and R waves are absent or small in the precordial leads.

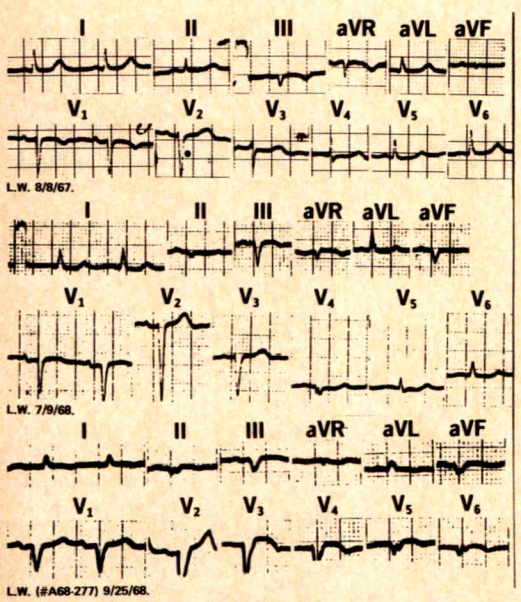

FIGURE 5. Electrocardiograms recorded over a 13-month period in a 53-year-old woman (A68-277) who had congestive heart failure for 5 months. The heart weighed 370 g. She died October 9, 1968. She had low voltage, left axis deviation, and absent R waves in the precordium. On the final electrocardiogram, the total 12-lead QRS voltage is 58 mm.

The hearts in 53 of the 54 patients were firm and rubbery, and this noncompliant consistency of the walls of all 4 cardiac chambers usually allowed the diagnosis of cardiac amyloidosis to be made immediately at necropsy without knowledge of clinical findings (Fig. 7 to 10). Both atria in all 54 patients on gross inspection were dilated, usually to a moderate degree. In contrast, the cardiac ventricles on gross inspection were of normal size in 43 patients (80%) and dilated in 11 (20%). The patients with dilated ventricles usually had other conditions that probably caused the dilatation: coronary heart disease

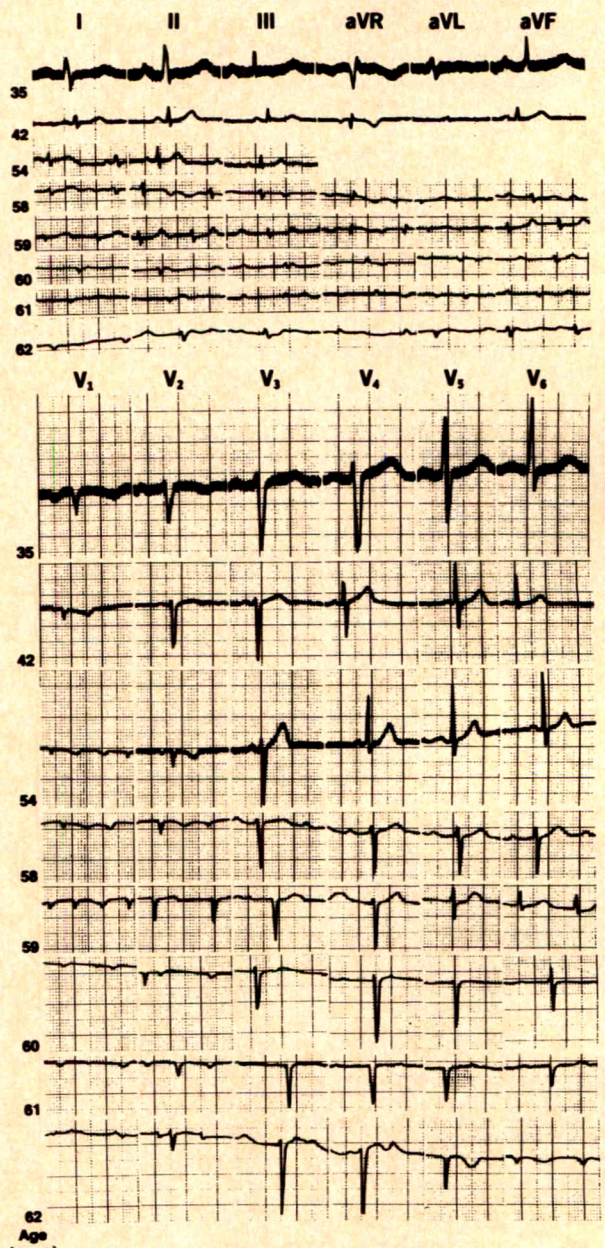

FIGURE 6. Electrocardiograms over a 27-year period in a 62-year-old man (GT 74A-259) who had congestive heart failure for 96 months and, at necropsy, a heart weighing 470 g. The QRS voltage progressively diminished, the axis changed, and R waves disappeared from the precordial leads. While taking digitalis, he developed atrial tachycardia with 2:1 block. The total 12-lead QRS voltage on the final electrocardiogram recorded 9 days before death was 79 mm.

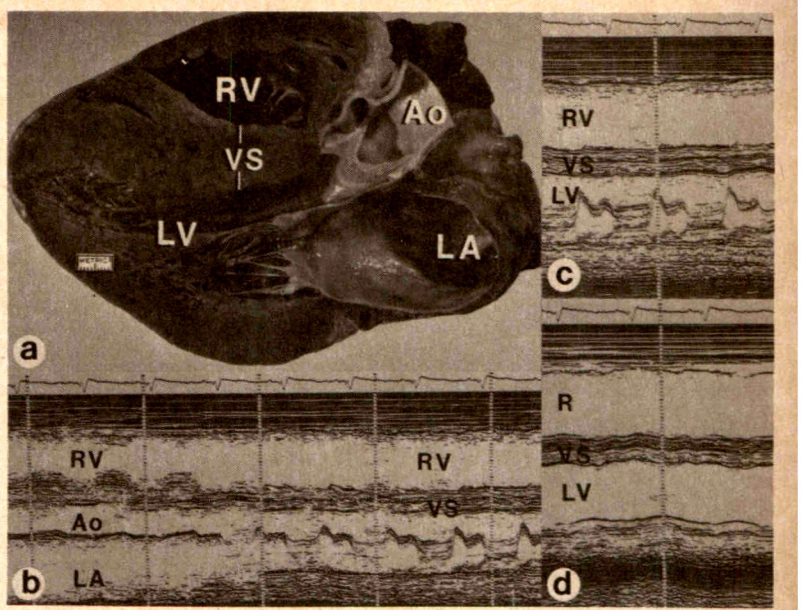

FIGURE 7. Cardiac amyloid with anasarca and pulmonary emboli. Longitudinal view of heart, weighing 545 g, in a 46-year-old man (A81-6) who had been well until 25 months before death, when parathesias and shoulder pain were noted. During his last 3 months he had severe congestive heart failure. When hospitalized 8 days before death, he had anasarca and third and fourth cardiac sounds. Electrocardiography showed a left atrial abnormality, right axis deviation, and poor R-wave progression over the precordium. Echocardiograms (**b, c, and d**) disclosed the ventricular septum (VS) and left ventricular (LV) free walls to be of similar thickness and each moved hardly at all. Both the left atrium (LA) and right ventricle (RV) were dilated. The pressures in mm Hg were: mean pulmonary artery wedge pressure, 27; pulmonary artery, 60/30; RV, 60/16; left ventricle, 90/26; and brachial artery, 90/60. He died from ventricular tachyarrhythmias. The heart in a longitudinal axis view is shown in **a**. The myocardium had the typical firm, rubbery appearance of extensive amyloidosis. Several pulmonary emboli may be the explanation of the right ventricular dilatation. Ao = aorta.

with left ventricular transmural scarring or chronic lung disease. The maximal thickness of the ventricular septum was identical or nearly so to the maximal thickness of the left ventricular free wall in 50 patients (93%); in the other 4 (7%) the septum was >1.3 times thicker than the free wall.

By gross examination, amyloid deposits (focal, tan, and waxy-appearing) were observed (and confirmed histologically) in the mural endocardium of 1 or both atria in all 54 patients and in valvular endocardium of 1 or more cardiac valves in 46 patients (85%) (Fig. 11): in the leaflets of the tricuspid valve in 45 patients (83%), the mitral valve in 43 patients (80%), the pulmonic valve in 29 patients (54%), and the aortic valve in 29 patients (54%). In 27 patients (50%), amyloid deposits were observed grossly in the leaflets of all 4 cardiac valves.

Focal transmural left ventricular lesions were observed grossly in 9 patients (17%) (Fig. 8); on histologic examination the lesions consisted entirely of fibrous tissue in 7 patients (13%) and of amyloid deposits in 2 (4%).

At least 3 histologic sections of heart were examined in each patient. In every patient, at least 1 section of left ventricular wall and at least 1 section of atrial wall were examined. Amyloid deposits, readily identified on hematoxylin-eosin stains, were confirmed by either congo red or crystal violet stains or both. In the chamber walls, the amyloid deposits were located in (1) interstitium, that is, between myocardial fibers, not within them in all but 1 patient,[4] (2) endocardium, often of all 4 chambers but always of 1 or both atria in all patients, and (3) within the walls of several intramural coronary arteries in all patients (Fig. 12). Additionally, amyloid deposits often were found in the lumina of some intramural coronary arteries, causing severe (>75% in cross-sectional area) narrowing of some lumina. Despite numerous sections of the major epicardial coronary arteries, no amyloid deposits were observed. At least 1 and usually multiple cardiac valves contained amyloid deposits, but none were judged to have deposits of sufficient quantity to cause valvular dysfunction. In several patients in whom histologic sections included coronary sinus, amyloid deposits were visible histologically in the wall of this structure.

In all 54 patients, amyloid deposits were observed in 1 or more other body organs. No patient had amyloid limited to the heart.

TABLE III M-Mode Echocardiographic Observations in 11 Necropsy Patients With Fatal Cardiac Amyloidosis*

Case	Age (yr) & Sex	Interval (Days) Cath to Death	VS		LV Wall		VS/LV Ratio		LV Cavity		LA Cavity		Ascending Aorta	
			ES	ED	ES	ED	ES	ED	ES	ED	ES	ED	ES	ED
1	21F	90	14	12	21	14	0.7	0.9	20	36	28	22	24	20
2	40M	...	...	20	...	20	...	1.0	...	...	...	36	...	41
3	45M	15	28	24	18	15	1.6	1.6	24	32	...	58	...	...
4	46M	62	14	14	18	14	0.7	1.0	36	40	36	40	34	30
5	54F	...	...	20	...	20	...	1.0	...	...	...	36	...	41
6	55F	334	30	26	18	15	1.7	1.7	26	36	...	30	...	27
7	55F	150	25	24	26	20	0.9	1.2	29	33	35	30	40	38
8	62M	300	19	19	22	18	0.9	1.1	38	42	20	18	38	30
9	63M	15	35	25	25	16	1.4	1.6	...	...	...	...	...	...
10	78F	169	12	9	13	8	0.9	1.1	36	48	45	40	35	31
11	89F	13	20	19	18	10	1.1	1.9	55	65	45	42	35	32

* All measurements in millimeters.
Cath = catheterization; ED = end-diastole; ES = end-systole; LV = left ventricular; VS = ventricular septum.

TABLE IV Hemodynamic Data in 9 Necropsy Patients With Fatal Cardiac Amyloidosis

Case	Age (yr) & Sex	Interval (Days) Cath to Death	Right Atrium*			PAW*			RV* (s/d)	PA* (s/d)	LV* (s/d)	SA* (s/d)	CI (liters/min/m^2)
			a	v	m	a	v	m					
1	35M	90	...	...	11	...	...	25	52/16	48/28	100/24	100/70	...
2	38M	4	24	22	21	...	...	34	56/18	61/34	110/12	110/65	1.3
3	45M	14	12	13	11	28	38	30	60/11	65/33	100/28	100/64	1.7
4	46F	180	10	8	7	...	42	28	50/9	65/33	98/28	98/70	1.6
5	46M	360	...	...	20	...	...	27	60/16	60/30	90/26	90/65	...
6	47F	90	15	14	12	21	28	20	36/12	36/17	110/20	110/80	2.2
7	70M	7	...	...	...	...	...	30	50/	50/30	...	110/60	...
8	78F	150	14	11	10	...	30	26	70/2	70/30	100/20	100/60	2.3
9	96M	7	...	...	17	...	...	34	60/18	60/30	...	90/70	...

a = peak of a wave averaged for several beats; Cath = cardiac catheterization procedure; CI = cardiac index; LV = left ventricle; m = mean; PA = pulmonary artery; PAW = pulmonary arterial wedge; RV = right ventricle; SA = systemic artery; s/d = systolic/diastolic; v = peak of v wave averaged for several beats.

* Measurements in mm Hg.

Thrombi were observed grossly in 1 or more of the 4 cardiac chambers in 14 (26%) of the 54 patients: in 1 chamber only in 8 patients, in 2 chambers in 3 patients, in 3 chambers in 1 patient, and in all 4 chambers in 1 patient. Of the 22 cardiac chambers that contained thrombi (mainly fibrin in all) in the 14 patients, the right atrial appendage contained thrombi in 10 patients (isolated in 5); the left atrial appendage contained thrombi in 7 patients (isolated in 2); the right ventricle con-

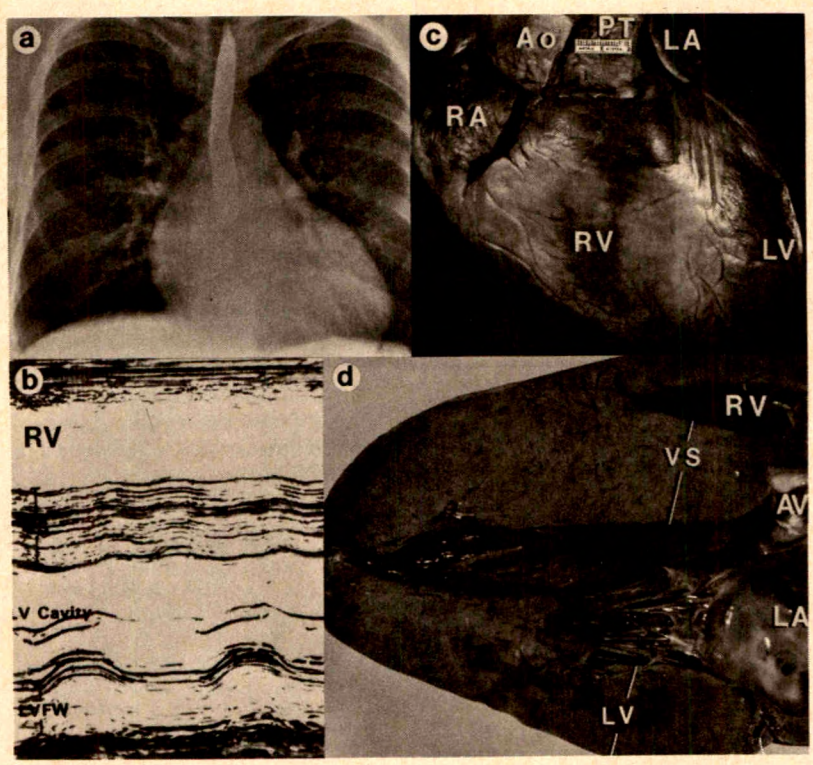

FIGURE 8. Cardiac amyloidosis simulating hypertrophic cardiomyopathy. Chest radiograph (**a**), M-mode echocardiogram just caudal to the tips of the mitral leaflets (**b**), exterior view of heart (**c**), and longitudinal axis view of heart (**d**) in a 46-year-old man (A79-25) who noted dyspnea while walking 24 months before death. M-mode echocardiography 1 month later disclosed the ventricular septum (VS) to be 1.7 times thicker than the left ventricular free wall (LVFW). The anterior mitral leaflet moved anteriorly during ventricular systole. The left atrial cavity was 30 mm in diameter. The pressures in mm Hg were: mean pulmonary arterial wedge, 5; pulmonary artery, 17/6; right ventricle (RV), 17/3; left ventricle (LV), 130/11; and aorta (Ao), 115/70. Clinically, the patient at that time was considered to have hypertrophic cardiomyopathy. Nine months before death, he had transient sudden left-sided weakness with slurred speech, worsened dyspnea, transient chest pain, and the carpal-tunnel syndrome was noted. Now the mean pulmonary arterial wedge pressure was 23; right ventricular pressure, 47/7; LV, 95/25; and Ao, 95/65 mm Hg. Echocardiogram now showed the ventricular septum to be 2.0 cm and the LVFW 1.5 cm; SAM now was absent. The left atrium (LA) now was 55 mm in diameter. A third catheterization performed 10 days before death showed the mean pulmonary wedge pressure to be 32 and that in the RV 65/11 mm Hg. The cardiac index was 1.4 liters/min/m^2. The heart was enlarged (**a**). M-mode echocardiogram (**b**) now showed the VS to be 2.6 cm and the LVFW 1.5 cm thick. Cardiac amyloidosis was never diagnosed clinically. At necropsy, the heart weighed 780 g. In addition to the usual interstitial myocardial amyloid, large deposits of amyloid were visible grossly on the LVFW (**d**). The VS is thicker than the free wall. The epicardial coronary arteries were virtually free of atherosclerotic plaques. AV = aortic valve; PT = pulmonary trunk; RA = right atrium; SAM = systolic anterior motion of the anterior mitral leaflet.

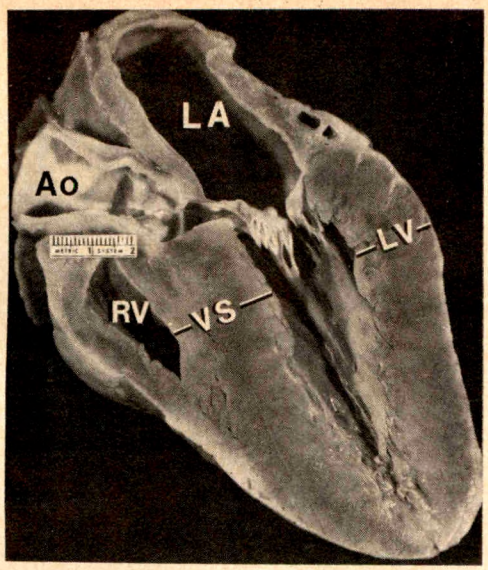

FIGURE 9. Cardiac amyloidosis simulating hypertrophic cardiomyopathy. Long-axis view of heart in a 55-year-old woman (WMC#A79-24) who had been well until 6 months before death when she developed periorbital purpura, pedal edema, and right-arm pain. When syncope occurred a month later, she was hospitalized and found to have multiple myeloma. Electrocardiography disclosed both atrial and ventricular arrhythmias and electrophysiologic studies disclosed distal H-V block. She never had congestive heart failure. On the day of death at home she fainted and soon thereafter had fatal cardiac arrest. The heart weighed 430 g and it had the typical amyloid consistency. A long-axis view is shown. The ventricular septum (VS) is thicker than the left ventricular (LV) free wall. The left atrium (LA) is dilated. Ao = aorta; RV = right ventricular cavity.

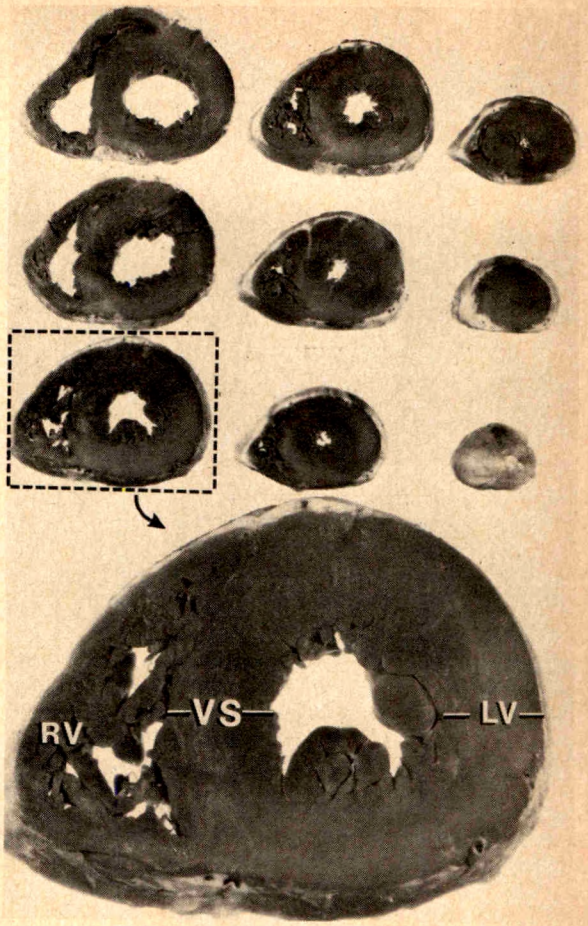

FIGURE 10. Massive ventricular amyloid deposits. Transverse cuts of the ventricles in the 49-year-old man (NNMC#A80-15), described in detail in Figure 3. This uniform appearance of the ventricular walls is the most common finding in extensive cardiac amyloidosis. LV = left ventricle; RV = right ventricle; VS = ventricular septum.

tained thrombi in 2 patients (none isolated), and the left ventricle contained thrombi in 3 patients (isolated in 2). Thus, of the 22 chambers with thrombi, 17 were atrial appendages and 5 were ventricles. None of the 5 ventricles containing thrombi appeared dilated by gross inspection. Of the 14 patients with intracardiac thrombi, 13 had clinical evidence of CHF and 1 died suddenly without evidence at any time of CHF: 2 (of 13) had chronic atrial fibrillation; 2 had clinical evidence of either pulmonary or systemic emboli, and 5 had severe narrowing of 1 or more epicardial cardiac arteries by either atherosclerotic plaque (4 patients) or fibrin-platelet embolus (1 patient). The latter patient was reported on previously.[2]

In addition to the extensive cardiac amyloid deposits, 8 patients (15%) had narrowing >75% in cross-sectional area by atherosclerotic plaques of 1 or more of the 4 major (right, left main, left anterior descending, and left circumflex) epicardial coronary arteries: in 5 patients, 3 of the 4 major arteries were so narrowed; in 1 patient 2 arteries, and in 2 patients 1 artery. The ages of these 8 patients ranged from 65 to 96 years (mean 78); 6 were men and 2 were women. Four had had periodic chest pain, considered angina pectoris in 2. One patient died suddenly and unexpectedly. At necropsy none had foci of myocardial necrosis, but 4 had healed transmural left ventricular infarcts, all of which had been clinically silent.

Calcific deposits were present in the mitral anulus in 7 patients (13%) and in 1 or more aortic valve cusps in 9 patients (17%). In 6 patients, the calcific deposits were present in both mitral anulus and in aortic valve cusps, in 3 patients they were limited to aortic valve cusps, and in 1 patient they were limited to mitral anulus. In 2 of the 9 patients with aortic valve calcium, the deposits appeared extensive enough to cause narrowing of the aortic valve orifice. In none of the 7 patients with mitral anulus calcium did the calcific deposits appear to cause clinically significant mitral dysfunction. All 10 patients (19%) with either mitral anular or aortic valve cuspal calcific deposits, or both, had calcific deposits in 1 or more of the 4 major epicardial coronary arteries, and in each patient they were within atherosclerotic plaques.

Discussion

Patients with cardiac amyloid deposits may readily be separated into 2 major groups: (1) those with amyloid deposits too small to produce cardiac dysfunction, and (2) those with amyloid deposits large enough to produce cardiac dysfunction which eventually is fatal. The finding of minute cardiac amyloid deposits in the heart in elderly persons at necropsy is common,[5–13] but patients with minute cardiac deposits, whether they be young or old, are not included in the present analysis. Each of our 54 patients had heavy cardiac amyloid deposits that caused fatal cardiac dysfunction. All but 1 had firm, rubbery ventricular and usually atrial walls with amyloid deposits in the interstitium (between myocardial cells) of the walls of all 4 chambers, in mural and usually in valvular endocardium, and in the in-

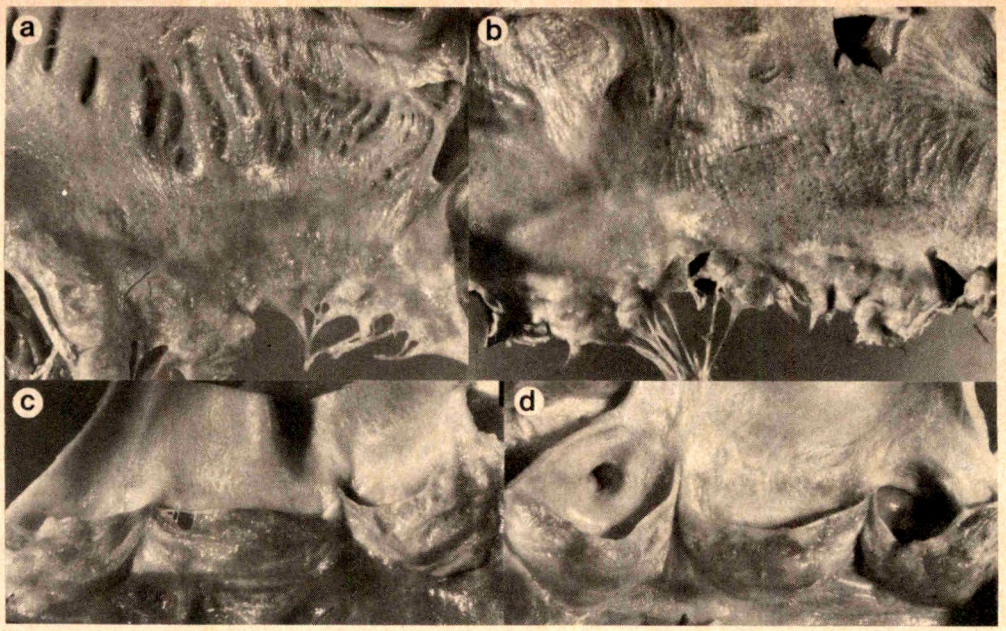

FIGURE 11. Endocardial amyloidosis. Opened right atrium and tricuspid valve (**a**), opened left atrium and mitral valve (**b**), opened pulmonic valve and pulmonary trunk (**c**), and opened aortic valve and aorta (**d**). The mural endocardium of each chamber and the cusps of all 4 cardiac valves contain amyloid deposits. The ventricular myocardium (shown in Figure 4) also contained massive quantities of amyloid, as did the pulmonary trunk. This 49-year-old man (NNMC#A80-15) had been well, but an automobile accident prompted an examination 10 months before death. Both pedal edema and hepatomegaly were found, the blood pressure was elevated (160/100 mm Hg), the heart was enlarged (cardiothoracic ratio 0.55), and electrocardiogram disclosed no R waves in leads V_1–V_3, nonspecific ST-T wave abnormalities, and low voltage. Echocardiogram was normal. Hepatic biopsy yielded amyloid. He remained asymptomatic until 4 months before death, when extensive subcutaneous edema appeared and pericardial effusion (700 ml) was found. The systemic blood pressure was then 120/80 mm Hg. His condition progressively worsened thereafter. He became acutely dyspneic at home and died.

FIGURE 12. Location of amyloid in myocardium (**a** and **b**), intramural coronary artery (**c**) and epicardial nerve (**d**). **a,** massive interstitial myocardial amyloid observed in a longitudinal section in an 89-year-old man (A69-259) with chronic congestive heart failure (CHF) and a heart weighing 520 g. In this section, more amyloid than myocardial fibers are present. **b,** massive interstitial myocardial amyloid observed in cross section in a 68-year-old man (H-A76-143) who had CHF for 36 months. **c,** amyloid occluding the lumens of intramural coronary arteries in a 67-year-old man (A69-187) with chronic CHF and a heart weighing 550 g. **d,** amyloid in epicardial nerves in a 74-year-old man (A58-190) who died suddenly from familial amyloidosis and had a heart weighing 700 g. (Hematoxylin-eosin stain [**a**] ×25 and [**d**] ×100; Movat stain [**b**] ×100; Masson stain [**c**] ×39, all reduced 25%.)

tramural coronary arteries. The 1 patient without interstitial myocardial amyloid had amyloid filling the lumina of most intramural coronary arteries.[3] Additionally, several patients had amyloid in the epicardium but never in the walls or lumina of the major epicardial coronary arteries. All our 54 patients with cardiac amyloid had amyloid deposits in 1 or more noncardiac body organs. We suspect that cardiac amyloid severe enough to cause clinical evidence of cardiac dysfunction is never limited exclusively to the heart.

Although a diagnosis of cardiac amyloidosis was established clinically in less than half of our 54 patients, most were studied clinically before echocardiography and radionuclide angiography became commonly performed procedures. Echocardiography is now often one of the first clues to the diagnosis of cardiac amyloidosis,[14–19] and myocardial technetium-99m pyrophosphate scintigraphy may be diagnostic of this condition.[20–23] Thus, cardiac amyloidosis severe enough to cause cardiac dysfunction almost surely will be suspected hereafter in a majority rather than in a minority of patients. Clinically, diagnosis of cardiac amyloidosis should be suspected in an older patient with evidence of CHF, poorly responsive and/or particularly sensitive to digitalis, unassociated with chest pain or systemic hypertension, and in the presence of cardiomegaly by chest radiograph but low voltage by electrocardiogram. The echocardiogram, rather than showing dilatation of the left ventricle, shows this chamber to be of normal or near-normal size and the ventricular walls to move poorly, and these findings can be confirmed by hemodynamic and angiographic studies.[24–27] Biopsy of either noncardiac or cardiac[28] tissue is required for absolute diagnosis.

Severe cardiac amyloidosis is 1 of the causes of spontaneous cure of systemic hypertension. Although nearly half of our 54 patients had had either a history of systemic hypertension or recordings of elevated systemic arterial pressures, or both, all had systolic systemic pressures ≤130 mm Hg and diastolic systemic pressures ≤90 mm Hg in the last 3 months of life. The average recorded peak systolic arterial pressure in the last 3 months of life in our patients was 102 mm Hg and the diastolic pressure was 70 mm Hg. Thus, if the systemic arterial pressure is elevated in a patient with CHF, the chance that the CHF is the result of cardiac amyloidosis is minimal. Additionally, none of our patients had evidence of left ventricular hypertrophy by electrocardiogram in their final 3 months, although several had had left ventricular hypertrophy by electrocardiogram >1 year earlier.

The length of time necessary to develop cardiac amyloid deposits extensive enough to cause cardiac dysfunction is uncertain. One clue to the amount of time required can be gained by study of the systemic arterial pressures over several years. We have now observed several patients with systolic systemic pressures in the vicinity of 180 mm Hg; during a period of 4 to 5 years this pressure gradually decreased to about 100 mm Hg without use of antihypertensive agents. Thus, a gradual but spontaneous decrease in systemic arterial pressure also might be a clue to the development of cardiac amyloidosis.

Cardiac amyloidosis needs to be added to the list of great cardiac masqueraders. Initially, it was cardiovascular syphilis that was stated to frequently simulate other cardiac conditions. In recent years, hypertrophic cardiomyopathy has become the most prominent masquerader. The QRS and T-wave changes on the electrocardiogram in cardiac amyloidosis are similar to those produced by healed myocardial infarction secondary to coronary atherosclerosis. The presence of a nondilated left ventricle and the presence of a ventricular septum thicker than the left ventricular free wall by echocardiogram has suggested the presence of hypertrophic cardiomyopathy. Five of our 11 patients with echocardiograms were suspected of having hypertrophic cardiomyopathy because of the combination of these findings. Simulation of cardiac amyloidosis clinically to pericardial constriction has long been recognized.[1,24–27] Three of our 54 patients underwent thoracotomy because of suspected pericardial constriction. Cardiac amyloidosis may present as pericardial tamponade.[29] Its delayed left ventricular filling may simulate mitral stenosis on rare occasions.[30]

Although amyloid deposits are always more extensive in "working" than in "conducting" myocardium,[1,31,32] arrhythmias and conduction disturbances are common (Table I). Some of these disturbances, however, may be the result of aging rather than the result of extensive cardiac amyloidosis.[13,33] In our patients, left-axis deviation (58%), atrial fibrillation (23%), and bundle branch block (18%) were common, but these also are relatively common in elderly patients without cardiac amyloidosis.[13,33] The frequency of low voltage (63%) and a healed myocardial infarction pattern (83%), however, was striking in our patients, and each of these should raise the possibility of cardiac amyloidosis in a patient with CHF of unclear cause.

This report provides for the first time measurements of QRS voltages in each of the 12 leads of an electrocardiogram in patients with cardiac amyloidosis. Simonson[34] provided data on the upper and lower limits of amplitude of the QRS complexes in each of the 12 leads in normal men and women aged 20 to 59 years. (The mean for normal subjects is not available.) The upper and lower limits of normal for men aged 50 to 59 years were 277 and 36 mm and for women 248 and 27 mm, respectively. The upper and lower limits of amplitude in all leads in 30 of our 54 patients (Table II) were 199 and 58 mm, respectively, and averaged 104 mm. For our 15 women from whom the data were available, the total 12-lead QRS voltage ranged from 58 to 199 mm (mean 109) and for our 15 men from 60 to 197 mm (mean 99).

In comparison, Siegel and Roberts[35] determined the total 12-lead QRS voltage in 50 patients (aged 16 to 65 years) with severe and fatal isolated aortic valve stenosis. The upper and lower limits of amplitude in all 12 leads in their 50 patients were 417 and 144 mm, respectively, and averaged 260 mm. In their 14 women with aortic stenosis, the total 12-lead QRS voltage averaged 277 mm and in their 36 men, 249 mm. The average heart weight of their 14 women with aortic stenosis was 521 g, and the heart weight in our 15 women with severe cardiac amyloidosis and available total 12-lead

QRS voltage was 494 g. The difference, however, in average total 12-lead QRS voltage (277 mm versus 109 mm) was a factor of 2.5 times. The mean heart weight of the 36 men with aortic stenosis studied by Siegel and Roberts[35] was 639 g and that of our 15 men with fatal cardiac amyloidosis and available total 12-lead QRS voltage was 570 g. The average total 12-lead QRS voltage in the 36 men with aortic stenosis, however, was 249 mm compared with only 99 mm in our 15 men with fatal cardiac amyloid, again a 2.5-fold difference. Thus, although the sum of the QRS voltage in leads I, II, and III may not fulfill criteria of "low voltage," that is, ≤15 mm, the total QRS voltage in all 12 leads in severe cardiac amyloidosis is usually considerably lower than normal, and particularly small in proportion to the weight of the heart.

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Cardiac Thrombosis and Thromboembolism in Chronic Chagas' Heart Disease

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A retrospective study of Chagas' heart disease was carried out by a review of 1,345 autopsy reports, with special reference to cardiac thrombus and thromboembolic phenomena. The incidence of cardiac thrombus was higher in cases of heart failure (36%) than in cases of sudden death (15%), higher in heavier hearts, and unrelated to age or sex. The left- and right-sided cardiac chambers were equally affected by thrombus. Endocarditis and blood stasis were considered important factors in the pathogenesis of cardiac thrombus. Thromboembolic phenomena were more common in the systemic circulation but caused relatively more deaths by pulmonary embolism. Fourteen percent of patients with thromboembolic phenomena died from them. Patients with multiple thromboembolic phenomena had a higher risk of death from embolism. Cardiac thrombosis or thromboembolic phenomena, or both, were present in 44% of the cases studied. Prophylactic measures should be taken for these important complications of Chagas' heart disease.

The difficulties involved in the prevention and treatment of thromboembolic phenomena are well known, especially in terms of proper diagnosis of causative factors and consequences, both in the pulmonary[1] and systemic[2] circulation. Thromboembolic episodes are of particular importance in regions where Chagas' disease is endemic. In this respect, it is important to point out that Chagas' heart disease was once labelled an "emboligenic cardiomyopathy."[3] Pertinent studies in such regions, however, are limited in number and were mainly conducted in small samples.[4–6] The one exception, a detailed study[7] of 208 cases with special emphasis on thromboembolic phenomena and their consequences, was based on selected material (Chagasic patients with heart failure).

Large numbers of patients with Chagas' heart disease die suddenly, even though they never had heart failure and, at times, never had any previous symptoms.[8] This form of Chagas' heart disease is familiar mainly to pathologists. A detailed anatomopathologic study of sudden death[9] did not completely explore thromboembolic phenomena. The present study of 1,345 cases was carried out to clarify the sources and consequences of thromboembolic phenomena in Chagas' heart disease by comparing cases with and without heart failure, based on a retrospective examination of autopsy reports.

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Methods

Our routine procedure for examining hearts suspected to have Chagas' heart disease is to fill the heart with formalin after ligating the great vessels. After 24 to 48 hours of fixation, the heart is opened by a single cut from apex to the base. Collection of body fluids for the complement fixation test for Chagas' disease is also a routine procedure in all autopsied cases. The diagnosis of Chagas' heart disease was chiefly based on gross findings such as apical aneurysm, dilated pulmonary conus, cardiomegaly, right atrial appendage thrombosis, and "rosary bead" type epicarditis. The diagnosis was based on the presence of at least 2 of these lesions,[10] except for apical aneurysm, which in itself was sufficient.[11] Nevertheless, some cases required additional information such as clinical and serologic tests and histologic examination to confirm the diagnosis. Chronic myocarditis and fibrosis were present for all practical purposes in all cases of Chagas' heart disease.

Case selection: All autopsy reports of persons ≥10 years of age were examined (5,467 records). Patients reported as having Chagas' heart disease as the cause of death were preliminarily divided into 2 groups on the basis of the origin of

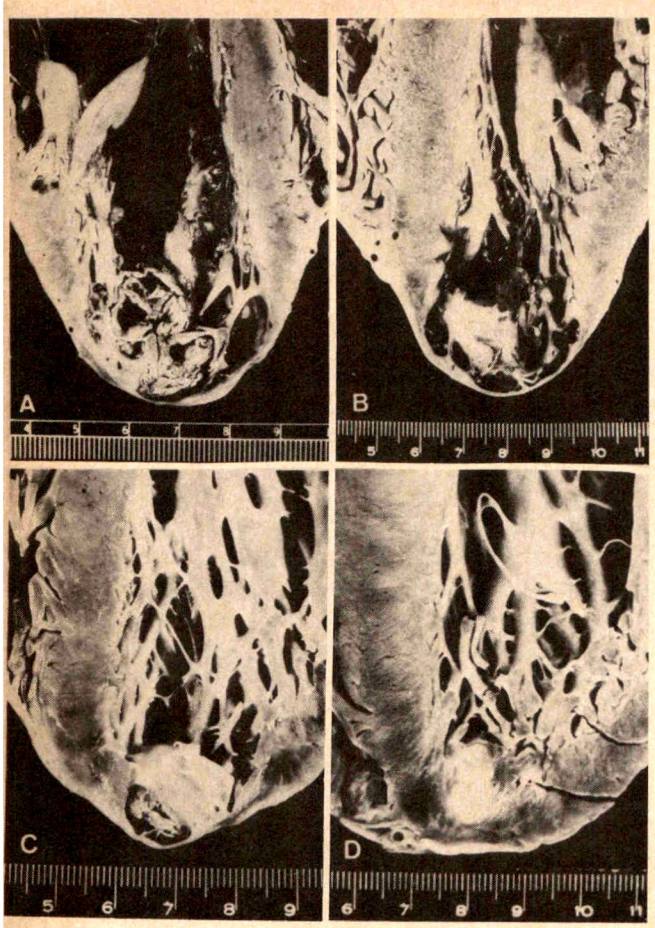

FIGURE 1. Cardiac thrombosis of the left apical region: with puriform softening (**A**) during different phases of organization (**B** and **C**) and completely hyalinized (**D**).

the autopsy request. Our department carries out postmortem examinations in (1) persons sent by hospitals at the request of a physician, and (2) persons who died a natural death without medical assistance, as required by law. Subjects in the first category are considered to have heart failure and subjects in the second to have sudden death (medically unattended, witnessed or unwitnessed).[12] All available information concerning these cases was then reexamined in order to exclude from the study: (1) cases included in the heart failure group without clinical or anatomic evidence of this condition, and cases in the sudden death group with evidence of heart failure; (2) cases presenting Chagas' heart disease in association with severe atherosclerosis, aortic aneurysms, or endocardial or valvular disease; and (3) cases with poorly documented evidence of Chagas' heart disease. On the basis of this second screening, approximately 20% of cases initially considered as Chagas' heart disease were excluded from the study, with a total of 1,345 cases remaining.

Although most of the autopsy reports were complete, occasionally some data such as age or heart weight were not available. These cases were excluded from the analysis of the feature not documented and for this reason there is a small variation in the total number of cases presented for each feature in the Results section.

Thromboembolic phenomena: The term *thromboembolic phenomena* is used in this report to designate infarction at different phases of evolution, including healing. It also designates recent embolism in cases where the interruption of blood flow was followed by death within a period not long enough to cause pathologic evidence of infarction in a given territory.

The search for deep vein thrombosis was not a routine procedure but was carried out in cases with pulmonary thromboembolic phenomena without right-sided heart chamber thrombosis. There were cases of pulmonary embolism with right-sided heart chamber thrombosis concomitant with vein thrombosis that was revealed either by clinical information or evident vein thrombosis; these cases are identified in the Results section.

Statistical procedure: The data were analyzed statistically by the chi-square test to assess independence between variables. Alpha values of <0.05 were considered significant. When appropriate, the comparison of 2 groups was performed by a test for difference between 2 proportions.

Results

The diagnosis of cardiac thrombosis is usually easily made at autopsy of Chagas' heart disease cases. Some thrombi, especially the apical ones, tend to hyalinize, and complete hyalinization of thrombi filling apical aneurysms may lead to an incorrect diagnosis of apical myocardial fibrosis as a primary lesion (Fig. 1). Ventricular thrombi occur almost exclusively in the apexes, and atrial thrombi in the atrial appendages.

Of 1,345 cases studied, 750 showed neither thromboembolic phenomena nor cardiac thrombosis. The remaining 595 cases (44%) presented the following features: thromboembolic phenomena with no thrombosis in the same side of the heart chambers (245 cases), only cardiac thrombosis (185 cases), or both thromboembolic phenomena and thrombosis in the same side of the heart (165 cases).

The incidence of cardiac thrombus did not differ by sex, was higher in cases of heart failure (Table I), and was unrelated to age (Table II). The left-sided chambers

TABLE I Cardiac Thrombosis in Cases of Chronic Chagas' Heart Disease, According to Sex and Mode of Death

Sex	Mode of Death	Thrombus		Without Thrombus	Total
		n	%		
Males	Heart failure	191	38	309	500
	Sudden death	65	16	349	414
Females	Heart failure	89	34	174	263
	Sudden death	24	14	144	168
Total	. . .	370	28	985	1,345

Male × female, chi-square = 1.41 (heart failure) and 0.18 (sudden death): both not significant. Sudden death × heart failure, chi-square = 75.98; significant. The proportion of thrombosis in cases of heart failure is significantly higher than in cases of sudden death ($z = 8.72$).

TABLE II Cardiac Thrombosis in Cases of Chronic Chagas' Heart Disease, According to Age

Age Range (yr)	Thrombus n	Thrombus %	Without Thrombus (n)	Total
<30	48	27	127	175
30–39	57	26	163	220
40–49	86	30	188	274
50–59	83	35	156	239
60–69	38	25	115	153
>70	18	26	51	69
Total	330	...	800	1,130

Chi-square = 7.32 (not significant).

of the heart were affected by thrombosis in 299 cases (the ventricle in 248 and the atrium in 51), whereas the right-sided chambers were affected in 280 cases (the ventricle in 86 and the atrium in 194). Table III shows the distribution of cardiac chambers affected by thrombosis. Heavy hearts were more affected by thrombosis than light hearts (Fig. 2).

The arterial beds most often affected by thromboembolic phenomena were lungs and kidneys, and the mortality rate due to such phenomena was mainly related to pulmonary and brain involvement (Table IV). The proportion of deaths directly caused by thromboembolic phenomena was significantly higher in cases with more than 1 arterial bed affected by thromboembolic phenomena: 25 of 247 cases with 1 arterial bed affected in contrast to 32 of 164 cases with more than 1 arterial bed affected (z = 2.70).

Discussion

The criteria used to initially separate heart failure and sudden death cases on the basis of hospital and police requests for autopsy were the basis of an initial screening that was subsequently refined using all available data as described in Methods. Less than 20% of the cases were eliminated during the second screening

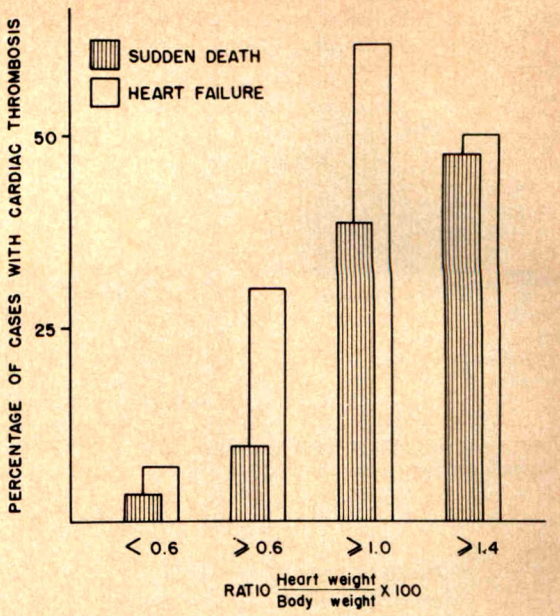

FIGURE 2. Cardiac thrombosis in cases of sudden death and heart failure according to the ratio heart weight/body weight ×100.

and none was transferred from 1 group to the other. Part of the reason for the effectiveness of the initial screening of the sudden death group was that most cases of poisoning and violent death were excluded by the police (that is, no autopsy was performed by our service) because these cases are required by law to be examined by a forensic pathologist. The few cases of poisoning or violent death that were encountered in our service were transferred to the forensic pathology service.

Cardiac thrombosis: The incidence of cardiac thrombosis in the 1,345 cases described here (27.3%) was lower than observed in other studies: 34% among 124 cases[6] and 76% among 208 cases.[7] These studies had been concerned exclusively with cases of heart failure. If we consider only the cases with heart failure in our

TABLE III Heart Chambers Affected by Thrombus in 1,345 Cases of Chronic Chagas' Heart Disease

Cardiac Chambers With Thrombus	Heart Failure (n)	Sudden Death (n)	Total	Percent of Grand Total
LV	82	39	121	33
RAA	56	22	78	20
LAA	6	3	9	2
RV	6	1	7	2
Total	150	65	215	58
LV + RAA	42	9	51	14
LV + RV	21	7	28	8
RV + RAA	10	2	12	3
RAap + LAA	7	2	9	2
LV + LAA	7	...	7	2
RV + LAA	1	...	1	...
Total	88	20	108	29
LV + RV + RAA	19	2	21	6
LV + LAA + RAA	8	...	8	2
RAA + LAA + RV	5	...	5	1
LV + LAA + RV	2	...	2	1
Total	34	2	36	10
LV + RAA + RV + LAA	8	2	10	3
Grand total	280	89	369	...

LAA = left atrial appendage; LV = left ventricle; RAA = right atrial appendage; RV = right ventricle.

TABLE IV Arterial Beds Affected by Thromboembolic Phenomena in Cases of Heart Failure and Sudden Death With and Without Cardiac Thrombus in 1,345 Cases of Chagas' Heart Disease

Arterial Beds	Heart Failure						Sudden death						Total		
	Thrombus			Without Thrombus			Thrombus			Without Thrombus					
	n	%		n	%		n	%		n	%		n	%	
Lungs	129	20	(17*)	57	9	(5*)	22	3	(4*)	19	3	(1*)	227	36	(27*)
Kidneys	109	17		62	10		20	3		35	5		226	36	
Spleen	43	7		28	4		7	1		10	2		88	14	
Brain	39	6	(11*)	21	3	(9*)	7	1	(1*)	...			67	10	(21*)
Limbs	9	1		4	1		...			1			14	2	
Small bowel	4	1	(1*)	4	1	(4*)	1		(1*)	2		(2*)	11	2	(8*)
Myocardium	4	1	(1*)	1			...			...			5	1	(1*)
Total	377		(30*)	177		(18*)	57		(6*)	67		(3*)	638		(57*)

* Number of deaths due to thromboembolic phenomena. The total number of thromboembolic phenomena was 640 detected in 412 cases. Twenty cases showing both venous thrombosis and pulmonary embolism were not included in the data presented in this table.

sample, the incidence of cardiac thrombosis (36.3%) is lower than that obtained in 1[7] of the series cited, which was carried out in a different region of Brazil (State of Bahia). Regional differences are suspected to exist in relation to the manifestations of Chagas' disease,[13] but this matter is still controversial.[14]

There was no difference in incidence of cardiac thrombosis between sexes in our study. Usually the pathologic consequences of Chagas' disease are more common among males, as indicated, for example, by the higher incidence of megaesophagus[15] and apical aneurysm.[11] Studies on rats have demonstrated that androgen administration aggravates infection by *Trypanosoma cruzi*.[16]

It is known that thrombosis of ventricular aneurysms caused by myocardial infarction occurs regardless of the time of onset of the necrotic episode[17] and that the thromboembolic phenomena occurring in rheumatic heart disease are more frequent among the elderly.[18] Furthermore, Chagas' heart disease has its onset early in childhood[19] and is an evolving disease.[20] However, contrary to what was expected, our data show that there is no difference in the incidence of cardiac thrombosis.

The distribution of thrombosis among the different heart chambers (Table III) was similar to that expected for a series of 208 cases.[7] The frequency of the most affected chambers agreed with that obtained in the smaller series, although discrepancies occurred with respect to less frequent locations and combinations.[6,21,22] The apical region of the left ventricle is a critical region in the Chagasic heart, where aneurysms, thromboses, or both occur with high frequency. A cause-effect relationship has been suspected for thrombosis and apical aneurysm.[23]

Ventricular thromboses were not very voluminous and it is doubtful that they alone could have led to heart failure, as previously reported for another type of thrombotic involvement of the heart.[24]

The myocardial hypertrophy that occurs in Chagas' heart disease is usually accompanied by dilatation, especially in the right chambers.[25] Heavier hearts had a higher frequency of thrombosis (Fig. 2). Indeed, it has been reported that blood stasis alone is unlikely to cause thrombosis.[26] Parietal endocarditis has been reported in Chagas' heart disease,[27] and may be a promoting or contributing factor in the genesis of cardiac thrombosis in Chagas' heart disease. As is the case for other heart diseases, blood stasis alone[22,27,28] or together with parietal endocarditis[29] is the mechanism thought to induce thrombosis in Chagas' heart disease.

Thromboembolic phenomena: The distribution of arterial beds affected by thromboembolic phenomena (Table IV) was similar to that described in a previous study on Chagas' heart disease[4] and to that detected in idiopathic congestive cardiomyopathy, although it differed from that reported for other types of heart disease[2,30] in the relative rarity of limb embolism. Since coronary embolism leading to myocardial infarction is relatively rare in all types of heart disease[31,32] it is interesting to note that 5 cases were detected in 1,345 cases studied.

The location of thrombus in the right atrial appendage in Chagasic hearts does not favor the detachment of emboli into the circulation, since there is little possibility for all the surfaces of a thrombus to be exposed to blood flow at this site.[33] This may be 1 of the reasons why systemic embolisms were more frequent in the material studied here.

It is not possible to determine with certainty the origin of an embolus in the pulmonary circulation detected in autopsy material, when cardiac thrombosis is present in the right chambers simultaneously with venous thrombosis. For this reason, those cases of Chagas' heart disease with both pulmonary embolism and venous thrombosis were excluded from the data presented in Table IV, but were reported in the footnote to the table. However, some investigators believe that the great majority of the pulmonary thromboembolic phenomena occurring in patients with Chagas' disease originate in the heart.[21,29] The systemic thromboembolic phenomena unrelated to cardiac thrombosis of the left chambers in our study were for the most part healed infarctions. A certain number of cases, however, consisted of recent processes, at times related to patient death. We do not believe that these thromboembolic phenomena without demonstrable cardiac origin should be considered to be cryptogenic,[33] since it is highly

possible that they arose from small cardiac thrombi released into the circulation.

Clinical implications: Obviously, deaths related to pulmonary thromboembolic phenomena are more prevalent than deaths related to systemic phenomena, since the latter are more frequent in the kidneys and spleen, where they are not lethal. A higher mortality rate occurs in patients with Chagas' heart disease with multiple thromboembolic phenomena. The recurrence of such episodes is potentially more dangerous.[34] For these persons, prophylaxis of the thromboembolic phenomena with anticoagulant therapy should be considered, especially since there is no contraindication for the treatment of patients with Chagas' heart disease. Prophylaxis by surgical therapy either by right atrial appendagectomy[35] or by apical aneurysmectomy[18] is not practical in view of the large number of patients with Chagas' heart disease. However, a few selected patients affected by arrhythmias whose disease could not be controlled by classic drug treatment have undergone left apical aneurysmectomy with good results,[36] both in terms of arrhythmia treatment and thromboembolism prophylaxis.

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Aortic Valve Closure and Cardiac Vibrations in the Genesis of the Second Heart Sound

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Simultaneous M-mode echocardiograms and external phonocardiograms were recorded in 15 healthy subjects to evaluate the genesis of the second heart sound. The onset of the second sound was found synchronous with the coaptation of the aortic valve cusps and a sharp vibration on the aortic wall. The closed valve was oscillating for 30 to 45 ms after the coaptation of the cusps. Magnified echocardiographic studies of the interventricular septum revealed a consistent, momentary quiver across the septal myocardium a mean of 4 ms after the onset of the second sound. In most subjects, a transient myocardial vibration was observed in temporal association with the first heart sound as well. The present observations suggest that the aortic valve closure initiates the production of the second heart sound, the main audible component resulting, however, from vibrations in the cardiac structures after the valve closure.

The exact genesis of the heart sounds is still a matter of contradictory opinions. Regarding the second sound, the major disagreement concerns the contribution of the aortic valve closure. According to the valvular theory,[1] the first component of the second sound results from the coaptation of the aortic valve cusps, and recent echocardiographic studies show that the onset of the sound coincides exactly with the aortic valve closure.[2,3] Other investigators maintain, however, that the aortic valve closes silently, and the second sound originates from aftervibrations in the cusps and in the walls and blood columns of the aorta and left ventricle.[4–6] The energy for these oscillations would come either from sudden deceleration of forward flow[4,5] or from abruptly arrested backflow of blood in the aorta.[6] The theory of silent aortic valve closure is vindicated by both animal[7–9] and human[10,11] studies which have demonstrated by various techniques that the coaptation of valve cusps precedes the onset of the second sound by a few milliseconds.

The aim of the present echophonocardiographic study was to ascertain the temporal relationship between the second heart sound and the aortic valve closure in normal subjects. Other possible echocardiographic correlates of the second sound were searched as well.

Methods

Subjects: The study group comprised 15 healthy men aged 23 to 30 years. They were selected from a large group of volunteers on the basis of a possibility of obtaining technically excellent left ventricular echocardiograms.

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Echocardiography: The ultrasonic examinations were performed using an Irex System II echocardiograph equipped with a 2.25 MHz medium focused transducer and a fiber optic stripchart recorder. The repetition frequency of the transducer was 1,000 impulses/second. An M-mode echocardiogram of the left ventricle was first recorded with the transducer on the standard interspace[12] to the left of the sternum and the ultrasonic beam directed just below the mitral valve tips across the left ventricle. Appropriately magnified M-mode echoes were recorded thereafter separately from the interventricular septum and the posterior wall without changing the transducer location and with only minor alterations in the beam direction relative to the heart. Finally, the transducer was angulated towards the right shoulder and M-mode studies of the aortic root valves were performed.

Phonocardiography: The phonocardiograms were recorded externally from the second intercostal space at the left sternal border with the use of an Irex heart sound microphone over a frequency range of either 250 to 2,000 Hz (6 dB/octave roll at the lower end) or 350 to 2,000 Hz (12 dB/octave roll at the lower end), or both. The recordings were performed simultaneously with the echocardiograms and a lead II electrocardiogram as black on white, thermally processed tracings at a speed of either 100 or 200 mm/s. The intensity of the records tended to be unacceptably weak when the higher speed was used, so most of the analyses were made on records taken at the speed of 100 mm/s.

Measurement technique: The time intervals between the onset of the second sound and its echocardiographic correlates were measured using an x-y digitizer and a PDP 11/30 computer. The absolute intervals were averaged from 5 consecutive cardiac cycles and made to the nearest even 5 ms corresponding to a measurement accuracy of 0.5 mm.

Results

Aortic studies: Acceptable aortic studies, with sufficient simultaneous visualization of the right and noncoronary cusps (Fig. 1), were obtained in 8 of the 15 subjects. The coaptation of the valve cusps coincided with the onset of the first vibration of the second heart

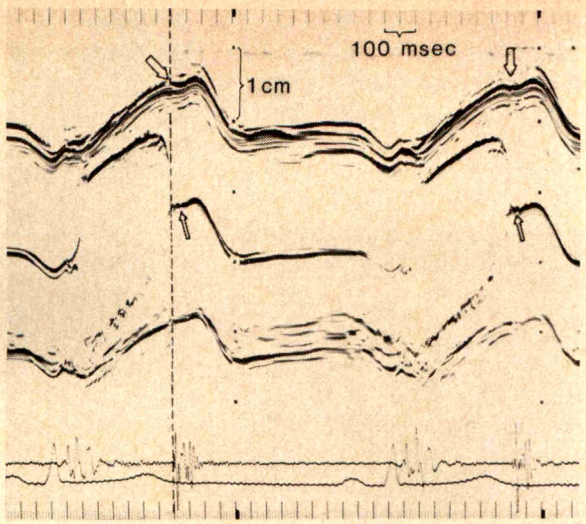

FIGURE 1. M-mode echocardiographic study of the aortic root demonstrating the simultaneity between the onset of the second heart sound and the aortic valve closure. Note also the coincident notch on the aortic wall and the aftervibrations in the closed valve (**arrows**). The chart speed was 100 mm/s.

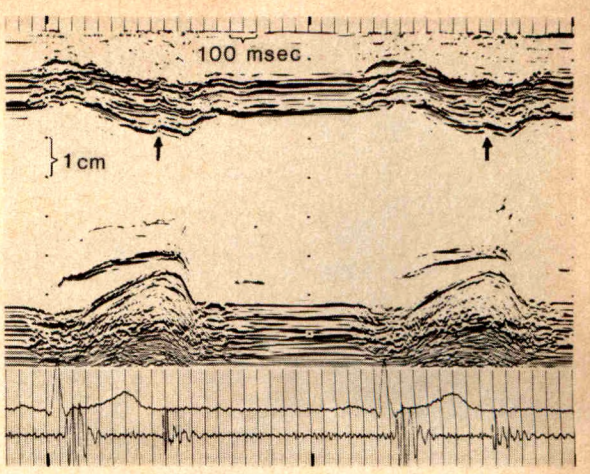

FIGURE 2. Standard M-mode echocardiogram of the left ventricle showing the sharp notch on the endocardial wave form of the interventricular septum (**arrows**). The chart speed was 100 mm/s.

sound; their time interval was 0 ms in each of these subjects. A sharp notch was invariably observed on the aortic wall occurring synchronously with the valve closure and the onset of the sound (Fig. 1). In most of these subjects, the closed aortic valve showed rapid vibrations lasting for approximately 30 to 45 ms after the point of collision of the cusps (Fig. 1).

Left ventricular studies: High-quality echocardiograms were obtained from the left ventricle and separately from the interventricular septum and posterior wall in each of the 15 subjects. The left ventricular studies demonstrated the presence of a septal notch in close temporal association with the second heart sound in each subject (Fig. 2). The magnified echocardiographic studies showed that, superimposed on the relatively smooth septal notch, there was a sharp, momentary quiver discernible not only on the endocardial echo but extending across the thickness of the septal myocardium (Fig. 3 and 4). The time interval from the onset of the second sound to the trough of the septal notch was 0 ms in 4 subjects and 5 ms in 11 subjects (mean 3.7 ms). In many of the latter subjects, the sharp peak of the notch coincided with the peak of the first high-amplitude vibration of the second sound. Magnified studies of the posterior wall showed in some subjects small inflections or discontinuities on the endocardial and myocardial echoes during the second sound. Yet, these were not distinct enough to allow their exact timing in relation to the phonocardiogram. Even though the genesis of the first heart sound was not specifically addressed in the present study, a relatively sharp septal quiver was noticed in most subjects in close temporal association with the first sound as well (Fig. 3B and 4).

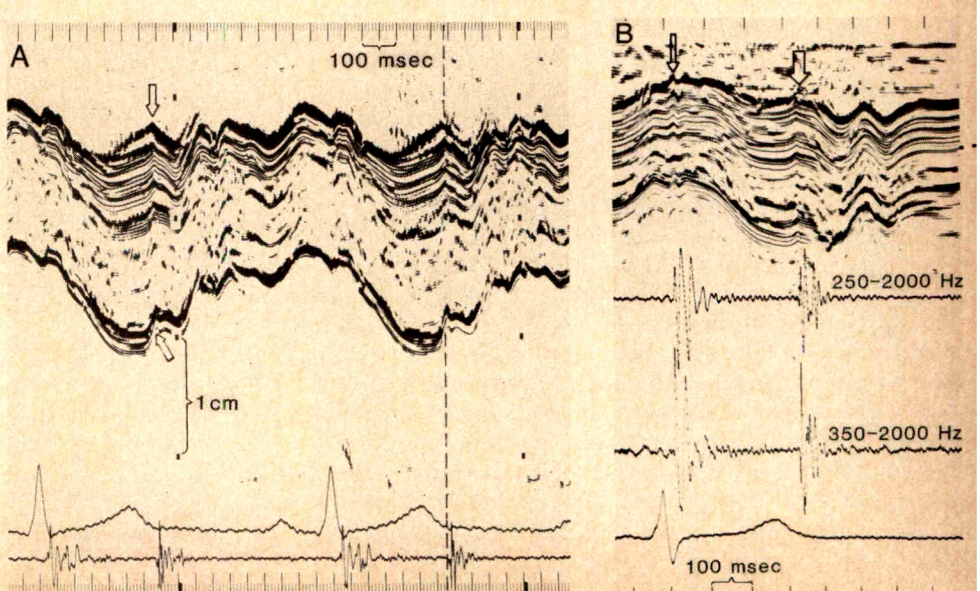

FIGURE 3. Magnified septal echocardiograms from 2 subjects (**A** and **B**) demonstrating the momentary myocardial quiver (**broad arrows**) immediately after the onset of the second heart sound. Note also the relatively sharp septal vibration during the first heart sound (**B, thin arrow**). The chart speed was 100 mm/s.

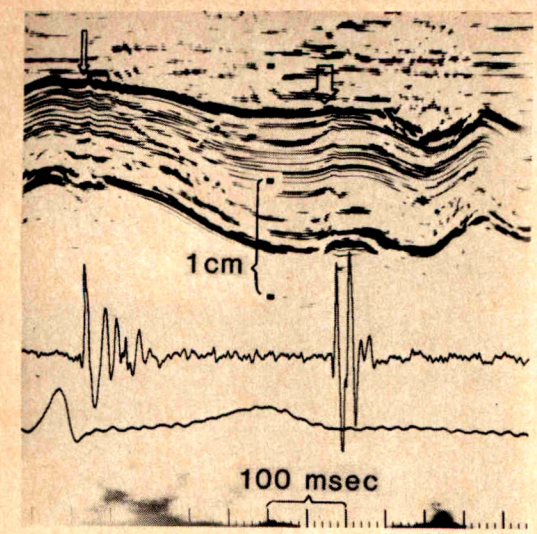

FIGURE 4. Magnified septal study at a chart speed of 200 mm/s from the same subject as in Figure 3B. The myocardial vibrations during the first and second sounds are clearly discernible (**arrows**).

Discussion

Methodologic considerations: In describing movements with time in the structures of the heart and great vessels, M-mode echocardiography provides in fact a kind of "phonocardiogram of reflected ultrasound." With a repetition frequency of 1,000 impulses/second, this technique should be able to detect correlates of the audible heart sounds even in their high-frequency range. This was verified in the present study when high-quality, magnified echocardiograms showed vibrations in the aortic valve and walls as well as in the ventricular myocardium in temporal association with the second heart sound. The most important limitation of the echophonocardiographic technique is that with a recording speed of 100 to 200 mm/s, the accuracy of measuring time intervals cannot be better than perhaps from 3 to 5 ms. This may be of significance since some investigators have claimed, on the basis of high-speed cineangiographic studies in dogs, that the onset of the second sound follows the aortic valve closure by an interval of only 0.5 ms.[5] It is self-evident that 2 events such a minute time interval apart would be interpreted as simultaneous by the present echophonocardiographic method.

Mechanism of the second heart sound: In spite of the aforementioned methodologic reservation, it proved rewarding to scrutinize the timing of the echocardiographic phenomena in relation to the phonocardiogram. The simultaneity between the onset of the second sound on the one hand and the coaptation of the aortic valve cusps and the coincident momentary vibration of the aortic wall on the other hand suggests that the valve closure indeed initiates the sound production. This observation agrees with some of the comparable earlier echocardiographic studies,[2,3] though not with all of them,[9–11] and supports the valvular theory about the genesis of the second sound.[1] Yet, the delay from the onset of the second sound to the momentary quiver of the septal myocardium, short as it was, suggests that the main audible component does not arise from the valve closure as such, but arises sooner from oscillations in the left ventricle immediately thereafter. Thus, the present findings agree also with those views maintaining that the second sound results mainly from vibrations in the "total cardiohemic system" after the aortic valve closure.[5,6,8]

The end-systolic septal notch: The septal notch described in the present study is not an entirely new finding. McDonald et al[13] reported in 1972 that the waveform of the echo from the left side of the septum has "a curious, notched appearance." They attributed this notch to a movement of the whole heart anteriorly during late systole and posteriorly during early diastole and postulated that a counterclockwise rotation of the heart was also contributory. Later, Assad-Morell et al[14] reported that the notch of the normal septal motion is associated in time with the end of the electrocardiographic T wave and with the carotid incisura. Also, they ascribed the notch to a twisting movement of the whole heart. Neither of these groups of authors recognized, however, the momentary quiver of the septal myocardium that is superimposed on the otherwise smooth-appearing notch and that relates to the genesis of the audible second heart sound, as likely as not. Interestingly, Sabbah and Stein[5] have found end-systolic notches on the left ventricular pressure tracing coincident with the components of the second sound. These pressure oscillations, which were observed both in humans and in dogs, to all appearance represent equivalents of the myocardial vibrations visualized echocardiographically for the first time in the present study.

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Analysis of the Amount of Tricuspid Valve Anular Dilatation Required to Produce Functional Tricuspid Regurgitation

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To determine the critical anular dilatation required for functional tricuspid regurgitation (TR) and the role of systolic anular shortening in the severity of TR, 67 patients in whom right ventriculography had been performed were studied. These patients were classified into group I, control (n = 12), and group II, patients with rheumatic valvular disease (n = 55). Group II patients were subclassified as follows: IIa, without TR (n = 19); IIb, with mild TR (n = 22); and IIc, with moderate to severe TR (n = 14). The angiographic maximal early systolic and minimal end-systolic diameters were measured. The shortening of the tricuspid anulus was expressed as percent reduction of the maximal diameter. The average maximal diameter (mm/m^2) was: group I, 21 ± 2; group IIa, 24 ± 2; group IIb, 31 ± 4; and group IIc, 37 ± 4. The average minimal diameter (mm/m^2) was: group I, 15 ± 2; group IIa, 18 ± 2; group IIb, 23 ± 2; and group IIc, 31 ± 3. The average percent shortening was: group I, 30 ± 7%; group IIa, 25 ± 7%; group IIb, 26 ± 5%; and group IIc, 15 ± 3%. The rheumatic patients had a larger maximal diameter than did those in the control group. Anular shortening was reduced only in the group with moderate to severe TR and preserved in the other groups, including those with mild TR. The critical diameter was determined to be between the maximal diameter in the rheumatic patients without TR and the minimal diameter in the patients with moderate to severe TR, or 27 mm/m^2. Thus this easily measured parameter can determine the presence and significance of functional TR, adding objectivity to the angiographic diagnosis of TR.

Better diagnostic methods[1–5] and surgical techniques for the treatment of tricuspid regurgitation (TR)[6–8] have increased the awareness of its frequency and its importance in the results of mitral valve surgery.[9,10] Although the postmortem and intraoperative direct observation of the tricuspid valve has shown a high percentage of organic lesions, functional TR remains common.[11,12] It is generally accepted that this is caused by anular dilatation secondary to right ventricular (RV) failure due to altered contractility, load, or both.[9,13] Tsakiris et al[14] experimentally and Tei et al[15] echocardiographically in human subjects have shown that the size of the normal tricuspid valve anulus does not remain constant during the cardiac cycle. Simon et al[16] recently reported that functional TR decreased or disappeared after mitral repair if the systolic shortening of the anulus improved. Our work was designed to determine (1) the critical point at which progressive anular dilatation produces TR, and (2) the role of systolic reduction of the anulus in the severity of TR.

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Methods

Patients: To study the dynamics involved in the closure of the tricuspid valve, 67 patients were selected out of the 265 consecutive patients in whom RV angiography had been performed following our previously described method.[5] This selection was based on certain criteria: (1) good quality angiograms were required together with the absence of premature ventricular contractions at the time of contrast injection; (2) patients with congenital disease, primary pulmonary hypertension, cardiomyopathy, or myocardial infarction were excluded; and (3) among the patients with rheumatic valvular disease and angiographic TR, all had to have undergone surgery and have an operative report confirming the absence of organic tricuspid disease (that is, cusp thickening or commissural fusion).

The average age was 48 ± 11 years (range 16 to 70); 34 patients were male and 33 female. These 67 patients were divided into 2 groups:

Group I—Control group: This group included 12 patients with sinus rhythm. Seven patients had a normal heart. Among

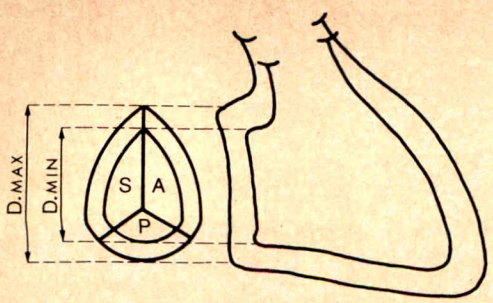

FIGURE 1. Diagrams of the right ventriculogram, frontal view of the tricuspid valve, and the measured maximal and minimal tricuspid diameters. A = anterior cusp, D. MAX = early systolic diameter; D. MIN = end-systolic diameter; P = posterior cusp; S = septal cusp.

the 7, 2 had functional murmurs, 3 had atypical angina, and 2 pulmonary disease. The other 5 patients had coronary disease without dyskinesia.

Group II—Rheumatic valvular disease: This group included 55 patients. According to the absence or presence and degree of TR they were classified into 3 further groups: *Group IIa:* Among these 19 patients without angiographic TR, 6 had mitral stenosis, 6 mitral disease, and 7 mitral and aortic disease. Fourteen patients had sinus rhythm and 5 atrial fibrillation. *Group IIb:* Among these 22 patients with mild TR, 7 had mitral stenosis, 9 mixed mitral disease, 5 mitral and aortic disease, and 1 aortic disease. All underwent surgery; after digital exploration the surgeon reported the absence of organic tricuspid disease. The functional TR was confirmed in only 9 patients. None of the 22 had the tricuspid valve repaired. Six patients had sinus rhythm and 16 atrial fibrillation. *Group IIc:* Among these 14 patients with a moderate to severe TR, 2 had mitral stenosis, 4 mixed mitral disease, and 8 mitral and aortic disease. All had the tricuspid valve repaired after confirmation of the absence of an organic lesion. All but 1 had atrial fibrillation.

Catheterization procedures: The patients were premedicated with diazepam (10 mg orally) 30 minutes before catheterization. A percutaneous femoral access was used in every patient for standard right- and left-sided cardiac catheterization. Pressures were measured at the mid-thoracic point with a Hewlett-Packard 1280 transducer and recorded with a Hewlett-Packard amplifier and recorder. Cardiac output was determined by the Fick method. All 67 patients underwent biventriculography. Fifteen minutes after left ventriculography, RV angiography was carried out following the method previously described by us.[5] Essentially it entails the use of a balloon catheter that becomes trapped in the trabeculae and, because of its ductility, does not induce false regurgitations. RV angiography was performed in the 30° right anterior oblique projection. Forty-five ml of 76% Urografin® (meglumine diatrizoate) was injected in 3 seconds with simultaneous recording of the electrocardiogram to detect the presence or absence of premature ventricular contractions. Filming was done through a Hiperlux Amplifier (CGR) in a Camaflex GV-35 mm camera at 50 frames/s. RV volumes were calculated with the Ferlinz method.[17] X-ray magnification was

TABLE I Hemodynamic Data

Group	RAP (mm Hg)	RA-V (mm Hg)	RV-EDP (mm Hg)	RV-SP (mm Hg)	PAP (mm Hg)	CI (liters/min/m^2)	TPVR (dynes s cm^{-5})
I: Control group (n = 12)	1 ± 0.7	2 ± 1	3 ± 2	24 ± 4	12 ± 4	2.92 ± 0.54	196 ± 66
II: Valvular disease							
IIa. Without TR (n = 19)	2 ± 2	3 ± 2	4 ± 3	36 ± 13	21 ± 9	2.43 ± 0.58	422 ± 236
IIb. With mild TR (n = 22)	3 ± 3	5 ± 3	4 ± 4	51 ± 33	31 ± 21	2.21 ± 0.47	738 ± 640
IIc. With moderate to severe TR (n = 14)	8 ± 5	11 ± 6	8 ± 5	57 ± 16	38 ± 11	2.31 ± 0.6	879 ± 362

Values are expressed as means ± standard deviation.
CI = cardiac index; PAP = mean pulmonary artery pressure; RAP = mean right atrial pressure; RA-V = right atrial V-wave; RV-EDP = right ventricular end-diastolic pressure; RV-SP = right ventricular peak systolic pressure; TPVR = total pulmonary vascular resistance; TR = tricuspid regurgitation.

TABLE II Angiographic Data

	Tricuspid Anulus			Right Ventricle		
Group	D max (mm/m^2)	D min (mm/m^2)	STA (%)	EDV (ml/m^2)	ESV (ml/m^2)	EF (%)
I: Control group (n = 12)	21 ± 2	15 ± 2	30 ± 7	76 ± 8	34 ± 6	55 ± 6
II: Valvular heart disease						
IIa. Without TR (n = 19)	24 ± 2	18 ± 2	25 ± 7	87 ± 20	48 ± 13	44 ± 7
IIb. With mild TR (n = 22)	31 ± 4	23 ± 2	26 ± 5	95 ± 31	56 ± 28	44 ± 9
IIc. With moderate to severe TR (n = 14)	37 ± 4	31 ± 3	15 ± 3	110 ± 26	71 ± 23	36 ± 9

Values are expressed as means ± standard deviation.
D max = maximal early systolic diameter; D min = minimal end-systolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; STA = shortening tricuspid anulus; TR = tricuspid regurgitation.

corrected by relating the catheter diameter to its radiographic diameter.

Analysis of RV angiograms: The degree of TR was graded as follows: *mild:* partial, nonhomogeneous opacification of the right atrium, including constant early or early mid-systolic regurgitations; *moderate:* almost complete and homogeneous filling of the right atrium; and *severe:* immediate filling of the whole right atrium and both caval veins.

In each RV angiogram the maximum diameter of the anular region of the tricuspid valve in early systole (D max) and the minimal diameter in late systole (D min) were measured (Fig. 1). These measurements were corrected in relation to the linear amplificaton of the angiographic image (CF). These values were related to the patient's body surface (BSA), so that diameter index (mm/m^2) = [D (mm) × CF]/BSA (m^2).

The systolic shortening of the tricuspid anulus (STA) was expressed as the percentage of decrease in diameter, related to the maximal diameter (D max): STA (%) = [(D max − D min)/D max] × 100.

To reduce the influence of the variable diastolic times in the patients with atrial fibrillation, these systolic measurements were performed only when the previous diastolic time was of 0.32 to 0.6 second.

To determine the critical anular dilatation beyond which TR always follows, it was assumed that it should be larger than the maximal diameter found in the patients without TR and smaller than the minimal diameter found in the patients with moderate to severe (pansystolic) TR.

Statistical analysis: The data were analyzed by standard statistical methods including one-way analysis of variance and the unpaired Student's *t* test. Tukey's method was used to compare multiple means if analysis of variance confirmed that at least 1 pair of means was significantly different.

Results

The more relevant hemodynamic data for each group of patients are presented in Table I. Table II summarizes the angiographic data for each group of patients.

The average maximal diameter of the control group (normal tricuspid function) was 21 ± 2 mm/m^2. This diameter was larger although without statistical significance in the patients with rheumatic valve disease without TR (group IIa). This increase in maximal diameter was much more evident among patients with TR (groups IIb and IIc) ($p < 0.01$). There was also a statistical difference between these last 2 groups ($p < 0.01$).

The average minimal diameter of the control group was 15 ± 2 mm/m^2. This diameter was larger in group IIa and even more so in group IIb. The largest diameter was found in the group with moderate to severe TR (group IIc). These differences among groups were statistically significant ($p < 0.01$). The average systolic shortening of the tricuspid anulus in the control group was 30 ± 7%. Although the average shortening in groups IIa and IIb was smaller, this finding had no statistical significance. The percent shortening in group IIc (moderate to severe TR) was 15 ± 3%, significantly lower than in all the other groups ($p < 0.01$).

Comparison of the end-diastolic and end-systolic volumes in the 4 groups showed significant differences ($p < 0.01$) only in the control group and the patients with moderate to severe TR (group IIc). The ejection fraction varied significantly between the control group and each group with rheumatic disease.

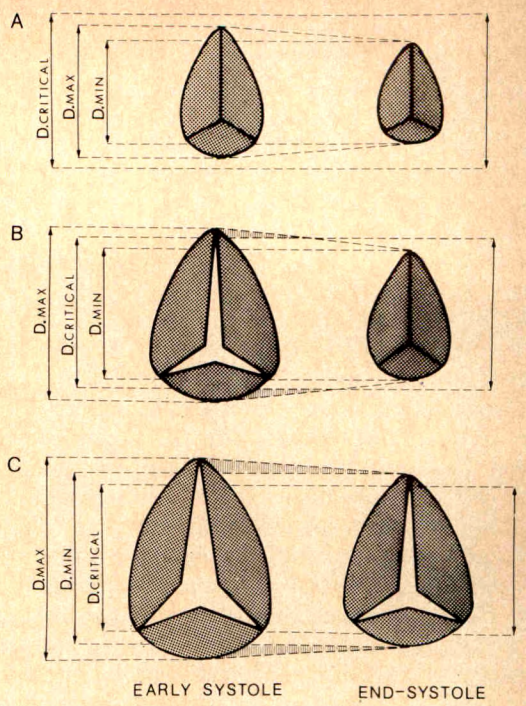

FIGURE 2. Diagram of the tricuspid valve in patients with rheumatic heart disease. **Panel A,** patients without TR (group IIa). Both maximal early systolic diameter (D. MAX) and minimal end-systolic diameter (D. MIN) are below the critical diameter. Cusp apposition is present throughout systole. **Panel B,** patients with mild TR (group IIb). D. MAX is larger and D. MIN is smaller than the critical diameter (D. CRITICAL). No cusp apposition during early and mid-systole occurs. **Panel C,** patients with moderate to severe TR (group IIc). D. MAX and D. MIN are above the critical diameter. No cusp apposition occurs. The **shaded areas** represent the systolic period during which TR is present.

The critical diameter above which regurgitation appears must be larger than the maximal diameter in those patients without TR, that is, the control and IIa groups. As the maximal diameter in group IIa is larger than that in the control group, the critical diameter must be higher than 24 ± 2 mm/m^2. This value is similar to the minimal diameter found in the patients with mild TR (group IIb, 23 ± 2 mm/m^2). This critical diameter must also be smaller than the minimal diameter found in patients with moderate to severe TR (31 ± 3 mm/m^2). Again, this value is similar to the maximal diameter in those with mild TR (group IIb, 31 ± 4 mm/m^2). Therefore, the critical diameter must be between 24 ± 2 and 31 ± 3. A working figure of 27 mm/m^2 is suggested. Figure 2 presents a schematic summary of our findings.

Discussion

Our angiographic measurements of the tricuspid anulus were very similar to those found by others.[1] However, we thought it would be more precise to relate them to the patient's body surface area (mm/m^2). These measurements represent only one of the tricuspid diameters and its variations during cardiac cycle in normal patients and patients with TR. The object of this work was not to determine the measurement of the tricuspid anulus circumference. However, if our measured max-

imal diameter is used to calculate the diastolic anulus circumference, this value corresponds with the previously reported postmortem studies[13,18,19] and with the echocardiographically calculated maximal circumference.[15] This is only so if it is assumed that in diastole the tricuspid orifice becomes circular. Conversely, the minimal circumference obtained from our minimal diameter cannot be similar to the reported echocardiographic values[15] because of the noncircular structure of the tricuspid orifice.

The anular dilatation in functional TR has been regularly reported in surgical and postmortem studies and accepted as the cause of regurgitation.[9,13] Tsakiris et al[14] showed in the dog and Tei et al[15] showed in man the role of anulus reduction in the normal tricuspid closure. The latter group also showed the anular dilatation and decreased area reduction in patients with TR. In an angiographic study, Simon et al[16] showed a relationship between postoperative improvement in the tricuspid anulus shortening and the reduction in functional TR. Furthermore, there must be a critical diameter above which TR follows due to the nonperfect coaptation of the leaflets. This critical closure diameter must be close to the largest maximal diameter found in patients without regurgitation. It must also be smaller than the minimal systolic diameter in patients with pansystolic regurgitation. This figure must therefore be between 24 ± 2 and 31 ± 3 mm/m^2: that is, between 26 and 28 mm/m^2. It can therefore be assumed that the critical diameter is approximately 27 mm/m^2. Given a ventricular pressure, TR is related to the incompetent orifice. This regurgitation starts at the maximal diameter and is progressively reduced until disappearing when the orifice reaches the critical diameter—that is, 27 mm/m^2. The larger the initial maximal diameter, the larger percent shortening required to achieve competence.

Our patients with a normal tricuspid valve and without altered contractility and load (control group) have smaller maximal and minimal diameters and larger percentages of shortening than any other group. The patients with rheumatic valvular disease but no TR (group IIa) had a slight dilatation of the tricuspid anulus or maximal diameter with a preserved shortening. As this maximal diameter is still below the critical diameter, no regurgitation ensues. The patients with mild and in many cases nonpansystolic TR (group IIb) had an anular shortening close to normal but with a large diastolic anular dilatation. Because of a satisfactory shortening, their minimal systolic diameter remained slightly larger than the maximal diameter in the normal patients but smaller than the maximal diameter in the rheumatic patients without TR (23 ± 2 versus 21 ± 2 and 24 ± 2 mm/m^2). All the latter figures are below the critical diameter. In this group the maximal diameter is above the critical diameter while the minimal diameter is below the critical diameter. The regurgitation cannot be pansystolic because sometimes during systole the shortening achieves a diameter below the critical figure.

The maximal diameter in the patients with moderate to severe TR (group IIc) was the largest of all groups and with a severe impairment in the percentage of shortening. The end-systolic or minimal diameter remained above the critical diameter, and therefore the regurgitation is present throughout systole.

The concept of critical anular dilatation simplifies the angiographic diagnosis of functional TR. If a measured systolic anulus diameter is above the critical value, then TR exists. If the late systolic diameter is above the critical value, this TR is moderate to severe. Second, the severity of the regurgitation will also be given both by the maximal diameter and the percentage of shortening of the anular region. When the maximal diameter is above the critical diameter TR exists, but its severity will depend on the capacity to shorten it below the critical value before the end of systole.

This method has the practical value of making more reliable the diagnosis of the presence and severity of functional TR. It eliminates the frequent pitfalls of previous angiographic methods such as quantification of right atrial opacification in the presence of variable right atrial sizes, premature ventricular beats, and altered right ventricular contractility. In these situations measurement of the anulus is always possible and therefore independent of these factors.

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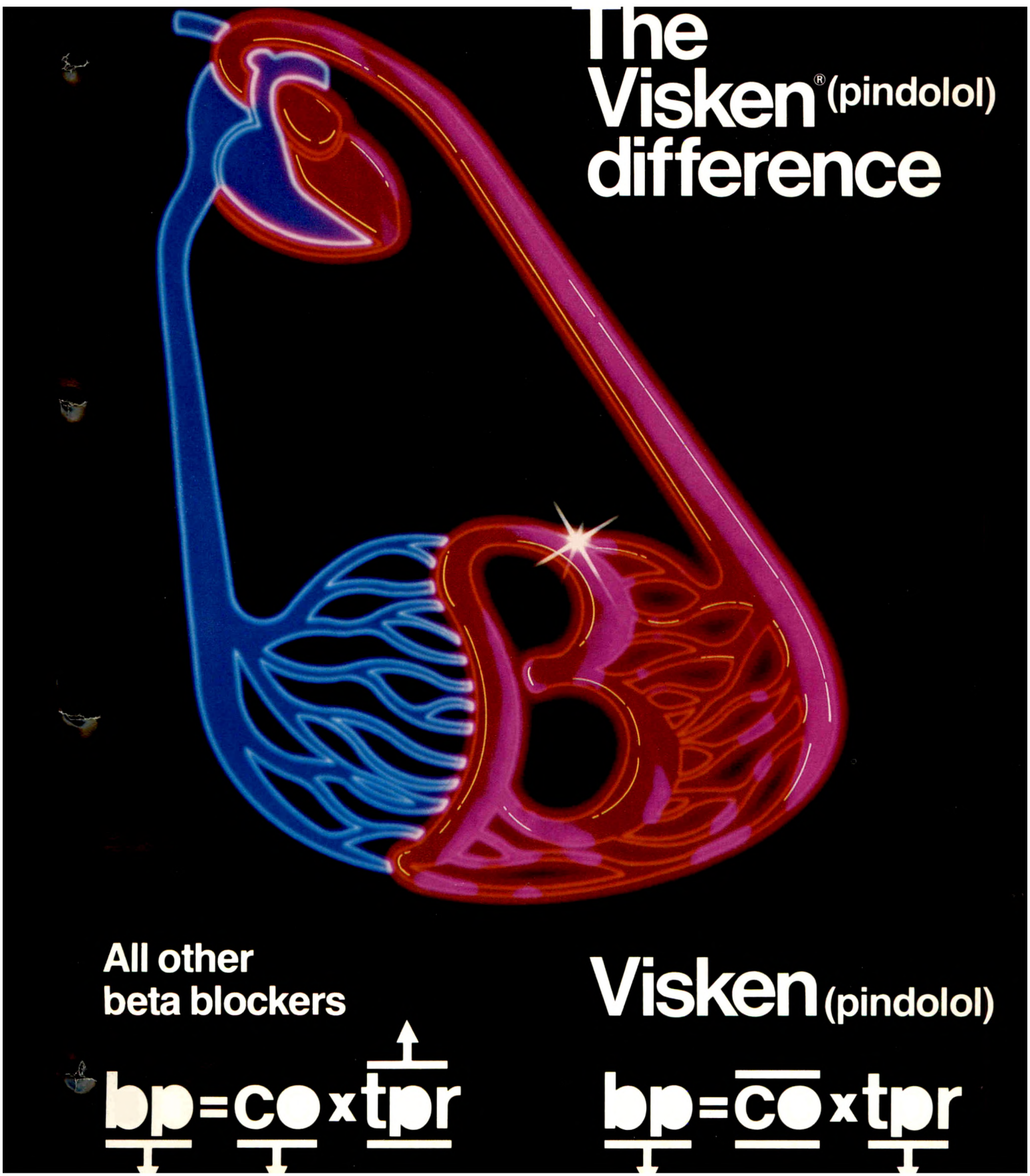
The Visken® (pindolol) difference
All other beta blockers
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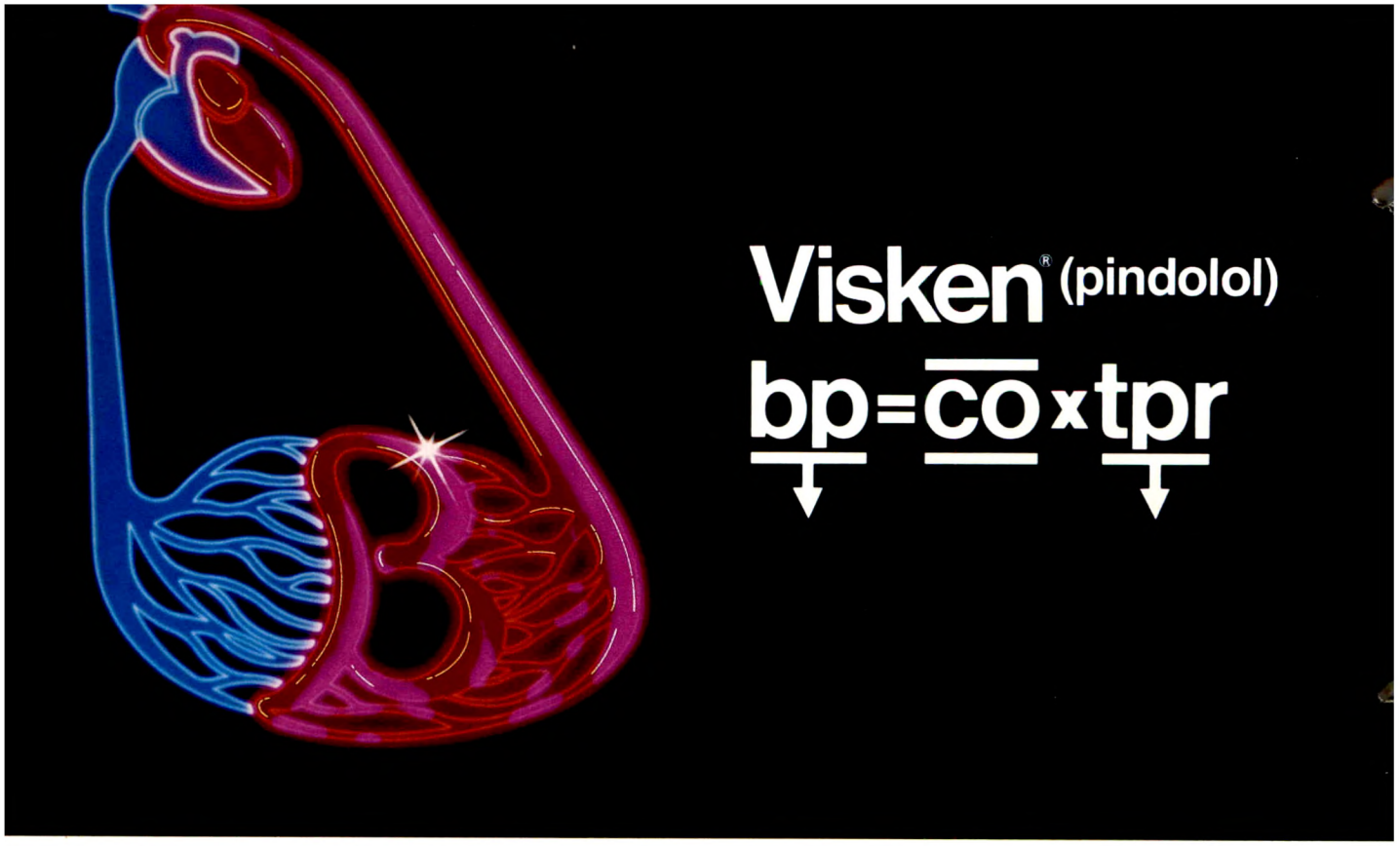

Makes hemodynamic sense in the treatment of hypertension

Reduces blood pressure

It's as effective as propranolol in normalizing blood pressure (dbp ≤ 90 mmHg) when used alone. It's also effective when used in combination with a diuretic.[1]

Has little effect on resting cardiac output

Unlike other beta blockers, Visken (pindolol) maintains resting cardiac output during long-term therapy. The clinical significance of this has not been evaluated.

Reduces total peripheral resistance*

Visken (pindolol) reduces one of the recognized components of hypertension: increased peripheral resistance.* Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]

Reduces exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

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*The clinical significance has not been evaluated. See clinical significance statement on facing page of this advertisement.

Has little effect on resting heart rate

Visken® (pindolol) produces minimal changes in resting heart rate. Average reduction: 4-8 beats/minute.

The clinical significance has not been evaluated

The clinical significance of maintaining resting cardiac output, resting heart rate and reduced total peripheral resistance has not been evaluated and there is no evidence or reason to believe that exercise cardiac output is less affected by Visken (pindolol) than other beta blockers.

Maintains renal blood flow

Visken (pindolol) reduces supine and standing blood pressure while maintaining effective renal plasma flow and glomerular filtration rates.[2]

Favorable side effect profile

Low incidence of bradycardia

Low incidence of cold extremities

Visken (pindolol) is contraindicated in:

1) bronchial asthma
2) overt cardiac failure
3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

*See clinical significance statement.

References:
1. Data on file, Sandoz Pharmaceuticals.
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Please see next page of this advertisement for brief summary of prescribing information.

Visken® (pindolol)

Available in 5 mg and 10 mg tablets

Convenient bid dosage

Dosage should be titrated on an individual basis.
Many patients respond to 10-30 mg a day in divided doses.

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE

Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS

Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS

Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS

Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY

Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS

Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

Body System/ Adverse Reaction	Total (Volunteered and Elicited) Visken (pindolol) (N = 322) %	Active Controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE

No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION

The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 10 mg b.i.d. alone or in combination with other antihypertensive agents. Many patients will respond to 15 mg per day (5 mg t.i.d.). The antihypertensive response usually occurs within the first week of treatment. If a satisfactory reduction in blood pressure does not occur within 2-3 weeks, the dose may be adjusted in increments of 10 mg per day at 2-3 week intervals up to a maximum of 60 mg per day.

HOW SUPPLIED

White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05). [VIS-Z2 9/1/82]

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VIS-383-1

Effect of Pericardiocentesis on Right and Left Ventricular Function and Volumes in Pericardial Effusion

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To assess the effects of pericardial effusion on ventricular performance and volumes, electrocardiographically gated blood pool cardiac scintigraphy was performed immediately before and after 14 pericardiocenteses in 10 patients, 7 men and 3 women, aged 28 to 73 years (mean 50). Cardiac tamponade was present in 5 patients. After removal of 140 to 1,100 ml of pericardial fluid (527 ± 305 ml [mean ± standard deviation]), left ventricular (LV) ejection fraction increased from 63 ± 5 to 64 ± 4% ($p > 0.05$) and right ventricular (RV) ejection fraction decreased from 47 ± 4 to 46 ± 2% ($p > 0.05$). LV end-diastolic and end-systolic volumes increased ($p < 0.01$) by 28 and 33%, and RV volumes by 40 and 43%, respectively. There were 8 patients with normal LV function (ejection fraction >60%) and 6 patients with subnormal LV function. Changes in ejection fraction were nonsignificant in the 4 subgroups. LV end-diastolic volume changes were more marked ($p < 0.01$) in patients with cardiac tamponade (+56%) than in those without tamponade (+17%), and in those with normal LV function (+36%) than in those with subnormal LV function (+21%). RV end-diastolic volume increased more markedly ($p < 0.05$) in patients with tamponade (+72%) than in those without tamponade (+23%), but were similar in patients with normal (+38%) and abnormal (+43%) LV function. After pericardiocentesis, RV volume increased more markedly than did LV volume. Thus, hemodynamic and clinical improvement after pericardiocentesis may be related only to an increase in stroke volume. RV and LV ejection fraction, a measure of myocardial contractility, was not affected significantly by the presence of pericardial effusion, even in those patients who had cardiac tamponade.

Although left ventricular (LV) function and volume changes produced by pericardial effusion have been assessed in many studies using experimental animal models,[1–5] studies in man have been limited.[6–9] No information is available regarding the effects of pericardial effusion on right ventricular (RV) function. Moreover, the results reported thus far have yielded conflicting results. LV ejection fraction (EF) was decreased,[1–4] increased,[5] or unchanged.[8] End-systolic dimension was relatively increased,[1,3] decreased,[5,8] or unchanged.[2,7] This study assesses RV and LV function and volumes before and after removal of pericardial fluid by means of the electrocardiographically (ECG)-gated blood pool cardiac scintigraphy.

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Methods

Patient population and study design: Consecutive patients undergoing therapeutic or diagnostic pericardiocentesis were included in this investigation if they had normal sinus rhythm and their clinical condition was stable. All studies included the following successive procedures: (1) duplicate acquisition of ECG-gated blood pool cardiac scintigraphy in the supine position after a 30-minute rest period; (2) pericardiocentesis and removal of as much pericardial fluid as possible; and (3) duplicate ECG-gated blood pool cardiac imaging acquisitions using the same patient and patient-camera positions as those used during the initial studies. Needle aspiration of pericardial fluid was performed using the subxiphoid approach under blood pressure and electrocardiographic monitoring. Patients did not receive intravenous fluids or medications during the study. Except for digitalis, all cardiac and vasoactive drugs were withheld for at least 24 hours before the investigations.

Radionuclide studies: Radionuclide studies were performed using standard equipment and techniques.[10] Briefly, each study consisted of 2-minute acquisition in the modified left anterior oblique projection. Analysis included the construction of variable ventricular regions of interest by an automated edge-detection algorithm for the left ventricle and a manual method for the right ventricle. Standard formulas were then used to calculate EF. The effects of pericardial fluid

TABLE I Clinical Data in 10 Patients With Pericardial Effusion During 14 Pericardiocenteses

Patient	Study	Age (yr) & Sex	Cause	Fluid Removed (ml)	Exp-Insp SBP (mm Hg) Before Per	Exp-Insp SBP (mm Hg) After Per	JVP (cm) Before Per	JVP (cm) After Per
			Cardiac Tamponade Present					
1	1	62M	Metastatic	1,050	25	15	>10	8
2	2	33M	Viral	380	20	8	>10	4
3	3	40F	Uremia	480	12	4	10	4
4	4	68M	Metastatic	1,100	15	0	>10	5
5	5	48F	Metastatic	220	50	12	>10	6
Mean ± standard deviation		50 ± 15	...	646 ± 403	24 ± 15	8 ± 6	>10	5 ± 2
			Cardiac Tamponade Absent					
6	6	43M	Uremia	295	10	4	7	5
7	7	56M	Uremia	580	8	4	10	4
8	8	73F	Metastatic	235	8	5	4	3
9	9	44M	Uremia	140	5	5	4	4
10	10	28M	Idiopathic	300	5	0	8	4
1	11	62M	Metastatic	780	8	0	11	6
4	12	68M	Metastatic	530	10	8	8	4
5	13	48F	Metastatic	815	10	0	8	4
7	14	56M	Uremia	475	5	0	5	4
Mean ± standard deviation		53 ± 14	...	461 ± 238	8 ± 2	3 ± 3	7 ± 2	4 ± 1

Exp = expiratory; Insp = inspiratory; JVP = jugular venous pressure (in cm) above the angle of Louis; Per = pericardiocentesis; SBP = systolic blood pressure.

drainage on relative ventricular volumes were quantitated using the formula: %VV change = $100 \times [(VC\ AP/e^{-\lambda t}) - (VC\ BP)]/VC\ BP$, where VV = end-diastolic or end-systolic RV or LV volume, VC = normalized (that is, corrected for the actual frame duration and the number of cardiac cycles processed) RV or LV end-diastolic or end-systolic counts after pericardiocentesis (AP) and before pericardiocentesis (BP), and $e^{-\lambda t}$ = general equation for isotope decay. A positive value indicates a larger volume after pericardiocentesis. There was a good correlation between the 2 values obtained at each stage for RV and LV end-diastolic and end-systolic counts before ($r = 0.89$) and after ($r = 0.94$) pericardiocentesis. The effect of pericardiocentesis on relative LV stroke volume was assessed by the formula: %SV change = $100 \times [(SC\ AP/e^{-\lambda t}) - (SC\ BP)]/SC\ BP$, where SV = LV stroke volume, SC = normalized LV stroke counts, AP = after pericardiocentesis, BP = before pericardiocentesis, and $e^{-\lambda t}$ = general equation for isotope decay. A positive value indicates a larger SV after pericardiocentesis.

Statistical analysis and definitions: Pre- and postpericardiocentesis data were compared using Student's *t* test for paired measurements. To determine the significance of the different response to pericardiocentesis among various subgroups, 2-way analysis of variance followed by the Tukey test was used. Cardiac tamponade was defined by the presence of increased jugular venous pressure, a paradoxical arterial pulse, evidence of pericardial effusion, and the disappearance or diminution of these clinical signs after the removal of pericardial fluid. Paradoxical pulse was defined as an inspiratory decrease in systolic blood pressure >10 mm Hg.

Results

Fourteen studies were performed in 10 patients, 7 men and 3 women, aged 28 to 73 years (mean 50) (Table I). Pericardiocentesis was carried out for therapeutic reasons in 13 instances and for diagnostic purposes in 1 (Patient 10). Patients in the former group complained of dyspnea and easy fatigability and exhibited elevated venous pressure or paradoxical pulse. Symptoms and signs improved or resolved after pericardial drainage. No complications occurred during this investigation.

Cardiac tamponade was present in 5 patients. There were 8 patients with normal and 6 patients with subnormal LV function as indicated by LVEF <60%[11] or segmental wall motion abnormality or both in either or both pre- and postpericardiocentesis studies. The amount of pericardial fluid removed varied between 140 and 1,100 ml (527 ± 305 mean ± standard deviation). After pericardiocentesis the mean heart rate decreased by 6 ± 5 beats/min and the average systolic blood pressure increased by 15 ± 10 mm Hg. These changes were more marked in patients with cardiac tamponade and in those with subnormal LV function (Table II).

Ventricular function and volume changes: Neither RVEF nor LVEF changed significantly after pericardiocentesis in the entire population as a whole or in any of the subgroups (Table II). Before pericardiocentesis, mean RVEF was higher in patients without cardiac tamponade and in those with normal LV function. However, average RVEF after pericardiocentesis was not significantly different in any of the subgroups.

Ventricular volumes, contrary to EF, increased significantly after pericardiocentesis (Table II). Both RV and LV end-diastolic and end-systolic volumes increased in all subgroups, but these changes were greater in patients with cardiac tamponade. The increase in LV end-diastolic and end-systolic volume was quantitatively more marked in patients with cardiac tamponade than in those without tamponade, and in patients with normal LV function than in those with abnormal LV function. The increase in end-diastolic volume after

TABLE II Effects of 14 Pericardiocenteses Performed in 10 Patients With and Without Cardiac Tamponade

	Tamponade		LV Function	
	Yes (n = 5)	No (n = 9)	Normal (n = 8)	Subnormal (n = 6)
Heart rate (beats/min)				
Before	108 ± 3	95 ± 2*	100 ± 2	96 ± 3
After	99 ± 1	92 ± 2	97 ± 2	90 ± 3
p	<0.001	NS	NS	<0.05
Systolic BP (mm Hg)				
Before	104 ± 4	120 ± 5*	120 ± 6	110 ± 7†
After	133 ± 5	128 ± 4	131 ± 6	130 ± 6
p	<0.001	<0.05	<0.05	<0.01
LVEF (%)				
Before	65 ± 8	62 ± 7	76 ± 3	47 ± 7†
After	69 ± 4	61 ± 6	74 ± 3	51 ± 6†
p	NS	NS	NS	NS
LVEDV change (in % units)	56 ± 9	17 ± 5*	36 ± 9	21 ± 9†
p	<0.001	<0.05	<0.01	<0.05
LVESV change (in % units)	69 ± 25	12 ± 10*	47 ± 26	14 ± 6†
p	<0.01	<0.05	<0.01	<0.05
LVSV change (in % units)	64 ± 8	15 ± 4*	41 ± 5	32 ± 6
p	<0.001	<0.001	<0.001	<0.001
RVEF (%)				
Before	43 ± 9	49 ± 2*	51 ± 4	42 ± 6†
After	45 ± 4	46 ± 2	47 ± 2	44 ± 3
p	NS	NS	NS	NS
RVEDV change (in % units)	72 ± 10	23 ± 6*	38 ± 11	43 ± 9
p	<0.001	<0.01	<0.05	<0.05
RVESV change (in % units)	69 ± 1	30 ± 6*	49 ± 11	38 ± 8†
p	<0.001	<0.01	<0.01	<0.01

* p <0.05 versus patients with tamponade.
† p <0.05 versus patients with normal LV function.
Data represent mean ± standard error of the mean.
p values are noted for data before pericardiocentesis versus those after pericardiocentesis.
After = after pericardiocentesis; before = before pericardiocentesis; BP = blood pressure; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; LV = left ventricular; NS = not significant; RV = right ventricular; SV = stroke volume.

pericardiocentesis was relatively larger in the right than in the left ventricle. LV stroke volume increased significantly after removing pericardiac fluid (Table II), and although patients with cardiac tamponade showed the more marked changes, an increase in LV stroke volume was seen in all patients during this investigation.

Discussion

The results of this study showed that the removal of pericardial fluid did not significantly change RVEF or LVEF even in patients with cardiac tamponade, whereas both RV and LV end-diastolic and end-systolic volume increased. Comparatively, larger volume changes were observed in the right than in the left ventricle. Patients with cardiac tamponade displayed the largest volume changes.

Few studies have assessed changes in LV function and volume after removal of pericardial effusion in man,[7–9] and none have defined RV function and volume changes. Firestein et al[7] found that in patients with small pericardial effusion, LV end-diastolic diameter was not significantly altered. Grose et al[8] and Settle et al,[9] studying patients with large pericardial effusion, reported that LV dimensions were significantly smaller before removal of fluid. The results of these previous studies are complementary rather than discordant. If the amount of pericardial effusion is minimal and its rate of accumulation slow, its effects on LV volume will be minor. If the amount of effusion is large or its rate of accumulation fast, or both, LV filling and volume will be most compromised. We studied patients with and without cardiac tamponade and thus found a spectrum of end-diastolic volume changes. It should be noted that patients with small pericardial effusion function in the initial, flat portion of the intrapericardial pressure-volume curve, allowing a large volume change without significantly affecting the intrapericardiac pressure. In contrast, patients with cardiac tamponade function along the steep portion of the pressure-volume curve and small volume changes will significantly alter intrapericardial and diastolic LV transmural pressure.[12] In addition, slow accumulation of fluid will permit "stretching" of the pericardium,[13] lengthening the flat portion of the intrapericardial pressure-volume curve. Thus, the degree of LV end-diastolic volume change cannot be predicted by the amount of pericardial fluid removed. In our study, some of the most dramatic increases in end-diastolic volume were seen after removal of relatively small amounts of fluid, and in general, patients with cardiac tamponade showed the largest end-diastolic volume changes.

RV end-diastolic volume increased in our patients after removal of pericardial effusion. This finding was

not unexpected because left and right ventricles are enclosed in the pericardial sac and thus both chambers are subject to the same external pressure. When the intrapericardial pressure increases as a result of pericardial effusion, the shifts in diastolic transmural pressure and diastolic volume will be in the same direction in both ventricles. Changes in RV end-diastolic volume were relatively larger than those in the left ventricle, a finding likely related to the more compliant right ventricle.[14] This observation is in keeping with previous reports.[15]

The reason patients with normal LVEF showed larger increases in end-diastolic volume after pericardiocentesis than did those with subnormal EF is not clear. A decreased EF, which indicates impairment of ventricular performance, is by definition associated with a rightward shift of the LV function curve, and an elevated LV end-diastolic pressure is commonly found. At a given intrapericardial pressure, patients with elevated LV diastolic pressure will have a greater net filling pressure than will patients with normal LV end-diastolic pressure. Thus, it is possible that the greater net LV filling pressure of patients with low EF may "protect" the ventricle from the compressive effects of pericardial effusion. Because intracardiac or pericardial pressures were not measured in this investigation, we have no information to establish whether or not this mechanism was operational.

The effects of experimental pericardial effusion and cardiac tamponade on LV end-systolic volume and contractility are matters of controversy. Various indexes of myocardial contractility were reported to be impaired in some studies[1–4] but not in others.[5] However, studies in man show more consistent results. Firestein et al[7] reported no change in LV end-systolic diameter or parameters or systolic function, whereas Settle et al[9] detected a decrease in end-systolic diameter. As just discussed herein, these results are not contradictory but complementary, as they apply to patients with a small amount of effusion and patients with pericardial tamponade, respectively. Our results agree with these clinical studies[7,9] and with the recent findings of Grose et al.[8] Discrepancies between experimental and clinical studies are likely due to the fact that pericardial effusion is created over a period of minutes in animal studies, whereas effusion in man often accumulates over several days, weeks, or months. Our results further support the concept that inotropic agents and therapeutic interventions designed to change the pre- or afterload[16,17] may be of limited value in the treatment of cardiac tamponade. Recently, dopamine and isoproterenol were found to have marginal beneficial effects, probably because these agents were unable to significantly reduce the already extremely small end-systolic volume in these patients.[18] Similarly, increasing the preload and reducing the afterload produced limited and nonsignificant changes in right atrial pressure, arterial pressure, and cardiac output.[19]

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Acute Effects of Phlebotomy on Right Ventricular Size and Performance in Polycythemic Patients With Chronic Obstructive Pulmonary Disease

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To assess the acute effects of phlebotomy on right ventricular size and performance, gated equilibrium radionuclide angiography was used to evaluate 10 patients with severe chronic obstructive pulmonary disease and erythrocytosis (hematocrit >55%). The mean right ventricular ejection fraction was abnormal before (0.38) but not after (0.43) phlebotomy, and the increase was highly significant ($p < 0.001$). Similarly, the right ventricular end-diastolic area decreased significantly from 588 to 505 pixels ($p < 0.02$). No significant changes occurred on the left side. Cardiac output was unchanged or slightly increased. Thus, assuming that afterload was unchanged, as reported by other investigators, the data herein are consistent with the hypothesis that a normalization in preload shifts the Starling curve, resulting in improved right ventricular performance with preservation of the cardiac output.

Severe chronic obstructive pulmonary disease (COPD) with its coexistent hypoxia, pulmonary hypertension, and occasional erythrocytosis, frequently leads to right-sided cardiac dysfunction. Although phlebotomy has been used for many years as therapy for the erythrocytosis seen in such patients, its short-term effects on right-sided heart size and performance have not been extensively investigated. Using a well-described gated equilibrium radionuclide angiographic method, we investigated the acute effects of venesection on right ventricular (RV) size and performance in 10 patients with severe COPD and erythrocytosis.

Methods

Patient selection: The study group consisted of 10 clinically stable men recruited from our pulmonary clinic, who were chosen because they had erythrocytosis (hematocrit >55%) secondary to COPD. No attempt was made to exclude patients with coexistent left heart disease, although no patient had clinical evidence of left ventricular (LV) failure (Table I). The mean age was 58 years. All patients had normal sinus rhythm. Eight patients had had carbon dioxide retention in the past and at least 7 had had episodes of RV failure. The control group consisted of 20 male physicians and staff who had no history of pulmonary or cardiac disease. The mean age was 40 years.

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Procedures

On the day of radionuclide testing, all patients underwent spirometry with use of a Collins Vitalometer (Braintree, Massachusetts) as well as arterial blood gas determinations.

Radionuclide techniques: The patients were studied before and immediately after venesection of 350 to 500 ml. In vivo labelling of red blood cells with technetium-99m using the method of Pavel et al[1] was performed. Radionuclide angiography was carried out with a gamma camera (Dymax MB, Elscint, Hackensack, New Jersey) equipped with medium sensitivity, 30° slant hole collimator directed caudally to enhance separation of the ventricular and atrial blood pools. All studies were performed in the left anterior oblique projection, which gave optimal septal delineation. Gated images were acquired using a minicomputer (Digital Equipment 11/34, Maynard, Massachusetts) in a 64 × 64 matrix at a rate of 25 frames for each R-R interval, for a total of 7.5 million counts.

Data analysis: Using the method of Holman et al[2] and standard gamma camera computer software (Gamma 11), we generated a time-activity curve from a region circumscribing the estimated LV blood pool. The end-diastolic and end-systolic frames were chosen and 2 functional images were generated: the ventricular and atrial stroke volume images. The end-diastolic frame minus the end-systolic frame produced an image in which each pixel registered the change in counts between diastole and systole, which was proportional

TABLE I Clinical Data in 10 Patients

Patient	Age (yr)	FEV_1	Hct (%)	Arterial Blood Gases			History			RVH by ECG	RVE by X-ray	PH by X-ray
				pH	PO_2	PCO_2	PCO_2 >45 torr	RV Failure	LV Disease			
1	55	0.4	58	7.34	40	55	+	+	0	+	+	0
2	61	0.5	56	7.40	42	62	+	+	0	0	0	+
3	62	0.7	59	7.43	48	40	+	+	0	+	+	0
4	59	1.2	56	7.39	63	45	+	+	0	+	0	+
5	56	0.6	60	7.46	62	36	+	+	0	+	0	0
6	64	1.0	60	7.43	56	47	+	+	H	0	0	0
7	67	0.7	57	7.43	82	33*	0	0	0	0	0	0
8	57	1.2	58	7.40	102	42*	+	0	H	0	0	0
9	54	1.3	62	7.41	62	47	+	+	0	+†	...	...
10	50	0.7	57	7.45	48	41	0	0	0	0	0	0
Mean	57	0.83	58	...	...	...	...	...	...	...	...	...

* With nasal oxygen.
† At necrospy.
FEV_1 = forced expiratory volume in 1 second (liters); H = hypertension; Hct = hematocrit; LV = left ventricular; PCO_2 = arterial carbon dioxide tension; PH = pulmonary hypertension; PO_2 = arterial oxygen tension; RV = right ventricular; RVE = right ventricular enlargement; RVH = right ventricular hypertrophy.

to ventricular volume change. Because of the phase difference between the atrial and ventricular volume curves, approximately 180°, subtraction of the end-diastolic image from the end-systolic image produced an atrial volume change image or paradox image. Superimposition of the ventricular and atrial stroke volume images resulted in a functional image which clearly delineated atrial and ventricular borders. With this composite image as a guide, we redefined the ventricular blood pools using a cursor. The ejection fraction (EF) for each ventricle was derived from another functional image: EF = (end-diastolic image − end-systolic image)/(end-diastolic image − background).

This method also included truncation of the superior aspect of the RVEF image in order to reduce atrial overlap and improve correlation with first-pass studies. The background was chosen automatically by an algorithm developed by Maddox et al[3] once the LV region had been approximated. Some operator discretion was permitted if background regions appeared inappropriate, such as over the spleen. Using this method, Holman found "excellent correlation between first pass and equilibrium studies in patients with both depressed and normal right ventricular function." His correlation coefficient was 0.95. The equilibrium RVEF was then corrected using the regression equation: $RVEF_{corrected} = 0.74\ (RVEF) + 0.03$.[2] The end-diastolic area was defined as the total number of pixels within the end-diastolic image, a reflection of ventricular volume that was independent of the concentration of radiolabel in the blood. A relative cardiac output was determined by multiplying the total number of counts contained in the LV region of the stroke volume image by the heart rate.[4]

Statistics: All group data are presented as means ± standard deviation. Student's *t* test for independent measures was used for comparison of groups. A *t* test for related measures was used to compare different studies performed in an individual patient. A p value <0.05 was considered significant.

Results

Spirometry and arterial blood gases: Results of spirometry (FEV_1) and arterial blood gas determinations performed at the time of radionuclide angiography are listed in Table I. The mean arterial oxygen tension in the patients breathing room air was 53 torr; 5 of the patients had an arterial carbon dioxide tension ≥45 torr.

Gated equilibrium radionuclide angiography: The mean RVEF among 20 normal control subjects was 0.48 ± 0.04. This was within 1% of Holman's normal control mean.[2] The mean resting RVEF of study patients before venesection was 0.38, significantly lower than the mean RVEF of normal control subjects (0.48), $p < 0.01$. The patient's mean RV end-diastolic area was 588 pixels, significantly higher than the control mean of 450, $p < 0.01$. The patients' mean LVEF was 0.59, which differed significantly from the control mean LVEF of 0.68 ($p < 0.05$). The patients' mean LV end-diastolic area of 777 was indistinguishable from the normal group mean of 686. Four of the 10 patients had a resting LVEF that was abnormal (<53%). Of those 4 patients, only 1 had clinical evidence of LV disease. All individual data are presented in Table II.

After the removal of 350 to 500 ml of blood, the patients' mean RVEF was 0.43 and RV end-diastolic area was 505 pixels; neither differed significantly from normal control values.

When the RVEFs in the study patients were compared before and after venesection, a significant increase was noted ($p < 0.001$). Similarly, when the pre- and postphlebotomy RV end-diastolic areas were compared, the ventricular size decreased significantly ($p < 0.02$) (Table II). No significant changes occurred on the left side. A relative cardiac output was calculated using the product of the total number of counts in the LV stroke volume image and the heart rate. The cardiac output did not change significantly after venesection. In order to assess the effects of radioactive decay and acute hemodilution on our cardiac output determination, we studied a single patient in the following manner. One ml of blood drawn during the prephlebotomy angiogram was counted in a gamma scintillation counter. It produced 6.37×10^6 counts/min immediately and 5.92×10^6 counts/min when recounted 30 minutes later during the postphlebotomy study. This 7% loss of ac-

TABLE II Equilibrium Radionuclide Angiographic Data Before and After Phlebotomy

	Before Phlebotomy					After Phlebotomy					
Patient	RVEF	RVEDA	LVEF	LVEDA	CO	RVEF	RVEDA	LVEF	LVEDA	CO	ACO
1	0.17	623	0.50	618	1.39	0.18	616	0.48	706	1.20	1.34
2	0.48	722	0.75	877	2.13	0.58	681	0.74	860	1.78	2.00
3	0.43	612	0.69	872	1.73	0.43	631	0.67	802	1.87	2.10
4	0.31	701	0.70	870	2.82	0.38	472	0.64	935	3.07	3.44
5	0.42	548	0.48	822	1.33	0.52	384	0.55	806	1.23	1.40
6	0.45	474	0.42	898	2.15	0.48	414	0.42	767	2.01	2.25
7	0.44	359	0.58	547	. . .	0.49	362	0.64	544	. . .	. . .
8	0.48	683	0.63	815	2.05	0.52	604	0.74	792	2.08	2.33
9	0.39	713	0.51	952	2.99	0.45	493	0.51	934	3.00	3.36
10	0.21	449	0.66	496	1.10	0.29	397	0.68	449	1.31	1.47
Mean	0.38*,‡	588*,§	0.59†	777	1.96‖	0.43‡	505§	0.61†	760	1.95	2.19‖
± SD	0.11	126	0.11	161	0.65	0.12	118	0.11	157	0.70	0.78
Normal Control Mean ± SD	0.48	450	0.68	686							
	0.04	91	0.08	96							
"Normal"	>0.39		>0.52								

* $p < 0.01$ (compared with control values).
† $p < 0.05$ (compared with control values).
‡ $p < 0.001$ (paired *t* test).
§ $p < 0.02$ (paired *t* test).
‖ $p < 0.05$ (paired *t* test).
ACO = cardiac output ($\times 10^6$ counts) when stroke volume counts increased by 12% to account for label decay and acute hemodilution; CO = cardiac output ($\times 10^6$ counts); EDA = end-diastolic area; EF = ejection fraction; LV = left ventricular; RV = right ventricular; SD = standard deviation.

tivity agrees well with the decay one would predict on the basis of a half-life of 6 hours. A second specimen of blood drawn during the postphlebotomy scan produced 5.60×10^6 counts/ml/min when counted immediately, which represents the 7% decay and some slight hemodilution (the hematocrit decreased from 57% to 56%). If one assumes a similar time interval and degree of acute hemodilution for all the patients and increases the stroke volume counts in each postphlebotomy study by 12%, a small but statistically significant increase in cardiac output is then seen (Table II). The EF and end-diastolic area calculations are independent of radiolabel concentration.

Intraobserver variability: All data analysis was performed by 1 individual and repeat determinations varied by <2%.

Discussion

Although first-pass radionuclide angiography has been used by several investigators[5–8] to evaluate RV performance in patients with COPD, equilibrium radionuclide studies in such patients are just beginning to be reported.[9,10] In general, these investigators found that one third to one half of patients with severe COPD have a decreased RVEF at rest and many have an abnormal response to exercise. In general, the principal difficulty with equilibrium methods has been the problem of right atrial and ventricular overlap. We attempted to solve the problem of chamber overlap by use of functional images to define the perimeter of the RV end-diastolic region of interest and by truncation of the superior aspect of the EF image which consists largely of infundibulum and pulmonary artery.[2]

There are limited data available concerning the acute effects of phlebotomy on RV size and performance in polycythemic patients with COPD. Using an indicator dilution technique, Schaanning and Sparr[11] described a significant decrease in the cardiac output of polycythemic COPD patients after venesection of 500 ml. In contrast, Gertz et al[12] described no change in pulmonary arterial pressure, pulmonary vascular resistance, RV end-diastolic pressure, or cardiac output after venesection in 6 patients with similar disease. They concluded that the only demonstrable change after venesection was a slight increase in the heart rate and a decrease in the arterial carbon dioxide tension. Similarly, Rakita et al[13] described the acute hemodynamic changes after venesection in COPD patients and concluded that the right atrial and RV end-diastolic pressures decreased significantly, but that there was no change in cardiac index, pulmonary arterial pressure, or pulmonary vascular resistance.

In our 10 patients, venesection produced an increase in RVEF (0.38 to 0.43, $p < 0.001$) and a decrease in the RV size (RV end-diastolic area 588 to 505, $p < 0.02$). Cardiac output did not decrease. If one assumes, as was found by Gertz,[12] Rakita,[13] and their co-workers, that venesection causes no acute decrease in the pulmonary arterial pressure, that is, afterload or pulmonary vascular resistance, our data are consistent with the hypothesis that a normalization in preload shifts the Starling curve, resulting in an increased RVEF with the preservation or improvement of the cardiac output. Brent et al,[14] using hemodynamic and first-pass radionuclide methods, recently documented that RVEF is determined in part by preload. We conclude that venesection produces favorable short-term hemodynamic changes in patients with severe COPD and erythrocytosis, although the duration of this effect is unknown.

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Left Ventricular Performance During Exercise: Response of Ear Densitogram Derivative

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The peak derivative of the ear densitogram (PD) has been shown to track left ventricular (LV) function during exercise. Measured as percent change in amplitude from resting control, PD in normal subjects slowly and consistently increased throughout exercise and to 2 minutes of recovery, followed by return to control level. In contrast, PD in patients with coronary artery disease rapidly increased only to 1 minute of exercise, with no significant subsequent increase. Expressed as a percent change from control, the response of normal subjects differs significantly from that of patients with coronary artery disease at 1 and 4 minutes of exercise, and 2 minutes of recovery. The PD increase in normal subjects from end-exercise to 2 minutes of recovery may be attributable to the heart rate decreasing faster than venous return, associated with LV ejection time, which is significantly shorter than heart rate-predicted values 2 minutes after exercise.

Several studies have shown the first derivative of peripheral pulse waves to be a reliable correlate of left ventricular (LV) function.[1–6] The first derivative of the aortic and brachial pressure curves and the carotid pulse have all been used to track cardiac function under various hemodynamic conditions. Recently, Nakamura et al[7] showed that the peak of the first derivative of the ear densitogram (PD) tracked several indexes of LV function including ejection rate, ejection fraction, stroke volume, and velocity of circumferential fiber shortening in patients with atrial fibrillation. In the cardiac catheterization laboratory we also have shown that changes in PD correlate well with changes in ejection rate.[8] Along with several previous studies in which the ear densitogram signal has proved very stable and reliable for monitoring systolic time intervals during all levels of exercise,[9–12] these results demonstrated that the PD can be used to continuously track global function throughout exercise.

The ear densitograph has several advantages for continuous (including beat-to-beat) physiologic monitoring[13]: (1) it is stable during conditions tending to produce motion artifact; (2) it is reproducible; (3) the sensor's application pressure is always the same; and (4) it is totally noninvasive, safe, and inexpensive. This study was designed to characterize the response of the PD to uninterrupted treadmill exercise in normal subjects and coronary patients, and to evaluate its use as an adjunctive method in exercise testing.

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Methods

Subjects: We investigated the response of the ear densitogram in 2 groups of subjects. Group I consisted of 13 men, 5 with normal coronary angiograms and 8 normal volunteers, who fulfilled 2 criteria: (1) normal history, physical examination, chest x-ray film, and electrocardiogram; and (2) negative exercise test (completed maximum Bruce protocol). Group II consisted of 8 men found to have >50% narrowing of at least 1 major coronary artery, who fulfilled 2 criteria: (1) none had myocardial infarction, valvular disease, or coronary surgery; and (2) none was taking any cardiac medication.

The small number of patients in this study was predictable because of the strict criteria requiring only patients who had undergone coronary angiography and were not taking any medication and the time frame (9 months) available (almost every patient undergoing angiography receives 1 or more medications). Of 738 consecutive patients referred during 9 months for electrocardiographic stress testing, this yielded only 17 men, 10 with >50% narrowing of at least 1 coronary artery and 7 with normal coronary angiograms. We were able to obtain recordings of the ear densitogram throughout all levels of exercise and recovery in 5 of the 7 subjects with normal coronary angiograms and 8 of the 10 patients with coronary artery disease. Although symptomatic patients with

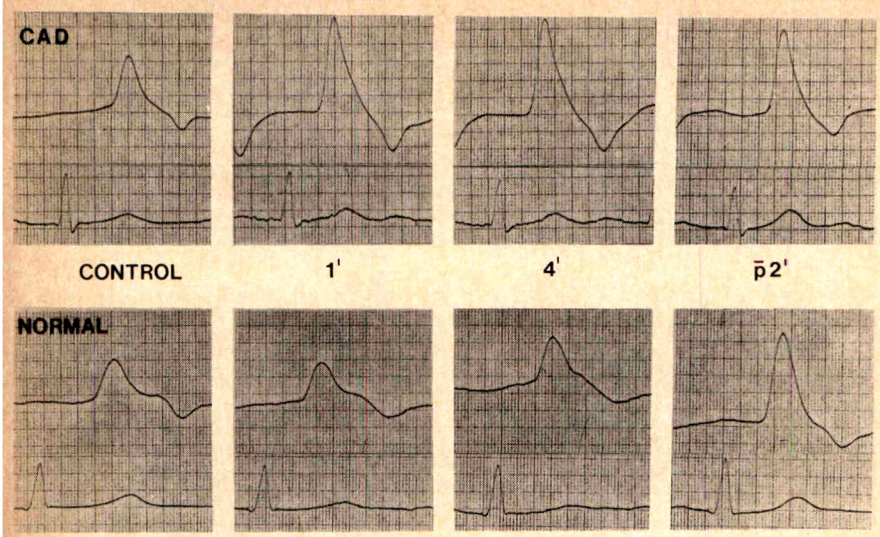

FIGURE 1. Representative densitogram traces from a patient in each group. **Top,** coronary artery disease (CAD). **Bottom,** normal subject. The times represented are control times and those times at which the results showed significant differences in mean responses between groups: 1 minute and 4 minutes of exercise and 2 minutes after exercise ($\bar{p}$ 2′).

normal angiograms may not be normal in the strictest sense, the results of noninvasive testing (exercise tests and systolic time intervals) in the 5 patients noted were also indistinguishable from those of 8 normal volunteers; these data were therefore consolidated for analysis.

The test was performed on a Quinton 18-54 treadmill without interruption at speeds of 1.7, 1.7, 2.5, 3.4, 4.2, and 5.0 mph; corresponding elevations were 5, 10, 12, 14, 16, and 18% (the first stage was 1 minute and all other stages were 3 minutes). The test was considered positive when there was ≥1 mm horizontal or downsloping S-T depression 80 ms after the QRS complex in 3 consecutive beats, and negative when the subject achieved >90% age-predicted maximal heart rate without that change.

The PD was obtained by filtering the signal from the ear densitogram (Hewlett-Packard model 780-16 earpiece, attached to the pinna of the ear as previously reported in detail)[13] through a Hewlett-Packard 7712 preamplifier with the low frequency cutoff set at 15 Hz. Recordings were made on a Cambridge model 3044B 3-channel stress test system at 100 mm/s. Control measurements were made after standing for 2 minutes. Subsequent recordings were made as patients were completing each stage. The end-exercise tracing was recorded immediately after exercise with the subject in the sitting position, as were the recovery recordings at 2, 5, and 10 minutes after exercise.

The measurements for obtaining heart rate, systolic time intervals, and the PD amplitude were aided by use of a Summagraphics digitizer coupled to a DEC-90 computer, with use of a program developed in this laboratory. Data were calculated from the mean of 5 consecutive beats for each recording as previously reported in detail.[13]

All statistical analyses were performed on the DEC-20 computer using the Bio Medical Data Program statistical package developed at UCLA.

Results

All patients in Group II and the 5 subjects with normal coronary angiograms in Group I had had chest pain consistent with angina pectoris. All 5 of those who proved to have normal coronary angiograms had negative maximum exercise tests (Bruce protocol). Results of exercise testing in Group II showed that only 3 of the 8 patients were judged to have a positive exercise test (2 mm S-T depression or elevation at 0.08 second after the end of the QRS complex) at end-exercise. One of these 3 patients had positive findings at 1 and 4 minutes of exercise with the test thereafter terminated. Of the other 2, 1 had negative findings at 1 minute and 4 minutes and the other showed 1 mm S-T elevation at 4 minutes, though negative at 1 minute. The other 5 patients in Group II had negative tests at 1 minute, 4 minutes, and at end-exercise.

Figure 1 shows representative densitographic curves in a patient in each group at the times when responses were statistically different, that is, at 1 and 4 minutes of, and 2 minutes after, exercise. Measurements of heart rate, preejection period, LV ejection time, and PD from control through the recovery period for Groups I and II are given in Table I. Except for differences at the end of exercise, the heart rate responses of Groups I and II are similar.

There were no significant differences in the control values of PD in the 2 groups. The normal group showed a slight but insignificant increase in PD at 1 minute of exercise, whereas the group with coronary artery disease showed a significant increase at 1 minute of exercise. When expressed as a percent change from control, the response of PD in the control group was significantly less than that of the coronary artery disease group at 1 minute of exercise ($p < 0.01$).

In all subsequent stages of exercise the normal group showed significant increases in PD. During recovery the normal group showed a further increase in PD from end-exercise to 2 minutes after exercise, followed by significant decreases toward control at 5 and 10 minutes after exercise.

Except for the increase in PD from control to 1 minute, the group with coronary artery disease showed only slight, insignificant increases throughout all subsequent stages of exercise. From end-exercise to 2 minutes after exercise, the PD showed no significant change in the coronary artery disease group. PD then decreased toward control values at the 5- and 10-minute postexercise levels. The 10-minute postexercise PD values for

TABLE I Mean Heart Rate (HR) and Systolic Intervals From Control Through End-Exercise to 10 Minutes After Exercise

	Control	1 Minute	4 Minutes	End-Ex	2 Minutes Post Ex	5 Minutes Post Ex	10 Minutes Post Ex
				Group I: Normal Subjects			
HR	76.31	95.00	104.53	154.30	106.76	99.07	93.84
±SEM	3.0	3.89	4.20	4.55	4.5	3.10	3.20
PEP	124.31	83.69	87.15	58.07	78.23	102.61	114.23
±SEM	2.78	2.62	2.61	2.61	4.64	3.23	3.80
LVET	244.53	262.00	252.69	186.69	213.00	247.15	256.61
±SEM	6.24	6.36	6.83	9.21	8.53	6.98	6.72
PD	13.92	15.08	16.31	15.77	30.23	23.31	16.81
±SEM	1.07	1.25	1.29	3.19	4.09	3.12	1.30
				Group II: Patients With Coronary Artery Disease			
HR	81.62	104.00	113.75	110.62	92.87	91.12	89.25
±SEM	6.2	6.14	7.31	10.76	9.92	5.06	6.25
PEP	125.00	83.25	75.75	66.00	79.12	94.37	107.50
±SEM	4.84	3.25	2.71	3.56	3.92	3.32	5.08
LVET	230.00	251.25	249.12	234.00	242.62	252.87	249.87
±SEM	8.75	8.95	9.20	16.00	13.61	9.85	10.19
PD	14.12	19.75	19.12	22.06	22.18	18.92	14.68
±SEM	1.60	2.58	1.93	2.24	2.41	2.40	1.82

Ex = exercise; HR = heart rate; PEP = preejection period; Post Ex = after exercise; LVET = left ventricular ejection time; PD = peak densitogram derivative; SEM = standard error of the mean.

TABLE II Densitogram Mean Peak Derivative (PD) and Change From Control (%ΔC) Through End-Exercise to 10 Minutes After Exercise

	Control	1 Minute	4 Minutes	End-Ex	2 Minutes Post Ex	5 Minutes Post Ex	10 Minutes Post Ex
				Group I: Normal Subjects			
PD	13.92	15.08	16.31	25.77	30.23	23.31	16.81
SEM	1.07	1.25	1.29	3.19	4.09	3.12	1.3
%ΔC	. . .	8.56	17.06	85.92	120.35	72.68	27.02
p*	. . .	NS	<0.01	<0.01	<0.05	<0.05	<0.05
				Group II: Patients With Coronary Artery Disease			
PD	14.12	19.75	19.12	22.06	22.18	18.92	14.68
SEM	1.61	2.58	1.93	2.24	2.41	2.40	1.82
%ΔC	. . .	39.55	39.20	62.53	59.51	34.36	6.72
p*	. . .	<0.01	NS	NS	NS	<0.05	<0.05

* Values indicate levels of significance for changes from preceding exercise stage.
NS = not significant; other abbreviations as in Table I.

both groups were not significantly different from control. The response of PD for each group is given in Table II. The p values indicate levels of significance for changes from the preceding stage. Figure 2 shows the percent change in PD from control throughout exercise in each group, and levels of significance for differences between groups.

Discussion

The PD appears to be a useful clinical tool for tracking LV function throughout exercise. The greater increase in PD from control in patients with coronary artery disease than in normal subjects at 1 minute of exercise is consistent with our previous report that the preejection period/LV ejection time (LVET) showed a greater reduction in abnormal than in normal subjects at 1 and 4 minutes of exercise.[10] These data are also consistent with the observations of Vatner et al,[14] who found initial improvement in LV function during exercise in dogs with coronary occlusion.

Other studies, demonstrating marked increase in end-diastolic pressure[15] and higher plasma levels of catecholamines[16] during exercise in patients with coronary artery disease, may explain this increased function observed in early exercise. Whatever the mechanism, the data presented indicate that the response of PD in early exercise tends to separate the control group from the coronary artery disease group.

Coronary angiography in the coronary artery disease group showed 2 with 3-vessel disease, 3 with 2-vessel disease, and 3 with 1-vessel disease. As judged by S-T segment response, 1 patient in each group had positive findings (with 1 of the patients with 2-vessel disease being the only subject who had positive findings at 1 and 4 minutes of exercise). Because of the necessarily small

TABLE III Recovery Period Ejection Times in 13 Normal Subjects

	Observed	Predicted*	Difference	p
End-exercise	186.7 ± 33.2	188.8 ± 19.7	2.13 ± 34.9	NS
2 minutes post	213.0 ± 30.7	245.8 ± 19.8	32.87 ± 17.8	<0.01
5 minutes post	247.2 ± 25.2	255.1 ± 13.4	7.95 ± 18.0	NS
10 minutes post	256.6 ± 24.2	261.3 ± 13.8	4.77 ± 19.6	NS

* Based on regression equation 374 = left ventricular ejection time + 1.2 heart rate.
NS = not significant.

numbers (for reasons given previously) of such patients, who despite angiography had no medication, expressions of sensitivity and specificity might be deceptive and we are reluctant to state cutpoints. Until we have larger numbers this report may be considered preliminary, documenting *trends* for this promising method (Fig. 2). Moreover, the pulse derivative cannot be individually calibrated at present so that these are relative changes. The largest such changes were seen at 1 minute ($p < 0.01$), at which time 7 of the 8 patients in Group II had mean values of percent change in PD of from 2 to $10\frac{1}{3}$ times the respective means in the normal subjects (Group I). Patient 8 deviated from Group I only at 2 minutes after exercise, when his percent change in PD was one half the normal mean.

In the normal group the continuous increase in PD throughout exercise is consistent with the expected increases in measurements shown to be correlates of PD: ejection rate, stroke volume, and contractility indexes reported in several other studies.[17–19]

The supplemental normal subjects were added to those with normal angiograms (Group I) on the basis of absence of history, physical examination, and electrocardiographic and stress test evidence of heart disease. Because they could not have undergone angiography, we have no absolute knowledge that some did not in fact have coronary lesions. However, on the basis of the noninvasive matching, they performed identically to the patients with chest pain and normal angiograms.

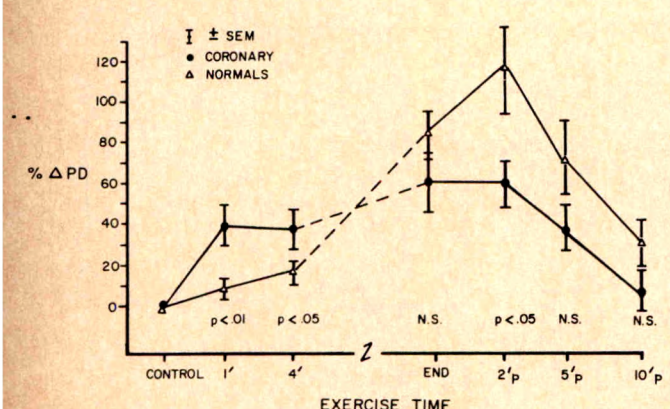

FIGURE 2. Trend chart showing changes from control as percent increases and decreases in peak derivative (% ΔPD). Mean differences are statistically different between patients with coronary artery disease (**black dots**) and normal subjects (**triangles**) at 1 minute and 4 minutes of exercise and 2 minutes after exercise.

Therefore, we are confident in supplementing Group I in that way. We have additional confidence in that method because each of these patients completed the Bruce protocol to individual maximum heart rate targets, whereas 7 of the 8 with positive angiograms could not achieve that.

The increase in PD from end-exercise to 2 minutes after exercise appears consistent with investigations reporting increased cardiac function in the recovery period. Cumming[20] noted an increase in stroke volume from peak exercise to 2 minutes after exercise. Reindell et al[21] postulated increased cardiac function 2 minutes after exercise based on increase in ratios of oxygen uptake to heart rate in the postexercise period. Stein et al,[22] using echocardiography, found increased end-diastolic volume and greater fractional fiber shortening during the recovery period, and Horowitz et al[23] noted an increased end-diastolic diameter during recovery from severe treadmill exercise in dogs. All these investigators conclude that the heart rate decreased faster than venous return during the recovery period, attributable to a classic Frank-Starling mechanism.

In the normal subjects the increase in PD from end-exercise to 2 minutes after exercise was associated with a decrease in the expected LVET, based on the standard regression equation LVET = 374 − 1.2 heart rate.[12] When differences between expected and observed LVETs were compared, the 2-minute postexercise LVET was consistently and significantly shorter than its predicted value, whereas the end-exercise and the 5-minute and 10-minute postexercise LVETs were not significantly different from expected values (Table III). Because all recovery recordings were made in the sitting position, this could not be a positional effect.

Because the 2 determinants of LVET are stroke volume and ejection rate, the disproportionately short LVET would indicate that either stroke volume is decreasing or ejection rate is increasing disproportionately from end-exercise to 2 minutes after exercise. The increased PD, which we have previously shown to correlate with ejection rate,[7] indicates that the latter phenomenon is most likely.

This increase in function, associated with a disproportionately short LVET in the postexercise period, would be a physiologically desirable response in that cardiac output would be maintained to meet metabolic demands, whereas the ventricles spend relatively less time in systole, thereby decreasing oxygen demand.

The coronary artery disease group showed no significant increase in PD from end-exercise to 2 minutes after exercise, nor was the difference between expected

and observed LVET 2 minutes after exercise significantly different from the other recovery period recordings. Comparisons between the 2 must be judged with caution, however, because of (1) the predictable individual differences in end-exercise times and end-exercise heart rates, and (2) the necessarily small groups owing to the rigid inclusion and exclusion criteria, that is, 17 (of 738 consecutive subjects) who had undergone arteriography but had no medication. More cases, including subgroups of patients with coronary artery disease, will be needed to extend this study from a pilot investigation and refine the clinical use of this postexercise response of PD.

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Effect of Cimetidine on the Pharmacokinetics and Pharmacodynamics of Quinidine

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The influence of cimetidine (1.2 g/day for 7 days) on the disposition and pharmacodynamic effects of a single oral dose of quinidine was studied in 6 normal volunteers. Cimetidine reduced the mean apparent oral clearance of quinidine (± standard error of the mean) from 25.5 ± 2.7 to 16.2 ± 1.4 liters/h ($p < 0.05$). This was reflected in a 55% (range 30 to 109) increase in the mean half-life from 5.8 ± 0.2 to 9.0 ± 0.6 hours ($p < 0.05$). Peak quinidine plasma concentrations and times to peak were also increased ($p < 0.05$). Plasma protein binding and urinary excretion of quinidine were unchanged by cimetidine treatment. Alterations in the pharmacokinetic variables of quinidine were mirrored in simultaneously measured electrocardiographic parameters. Changes in Q-T, rate-corrected Q-T, QRS, and R-R intervals after a single oral dose of quinidine sulfate (400 mg) were significant. Treatment with cimetidine potentiated these pharmacodynamic changes, but failed to achieve significant differences from quinidine alone. Thus, cimetidine impairs the elimination of oral quinidine in normal volunteers. This interaction may lead to quinidine toxicity in patients in whom cimetidine is concomitantly administered.

Cimetidine has gained widespread use in the treatment of peptic ulcer disease, with sales exceeding $500 million annually.[1] The extensive use of this H_2-receptor antagonist reflects the relatively infrequent and minor adverse effects observed in patients with normal renal and hepatic function.[2] However, recently cimetidine has been shown to reduce liver blood flow[3] and impair hepatic clearance of drugs such as warfarin,[4] benzodiazepines,[5] theophylline,[6] propranolol,[3] phenytoin,[7] and lidocaine.[8] This interaction has potential clinical significance for those drugs with a narrow therapeutic index, extensively cleared by hepatic metabolism.

Quinidine is an effective oral antiarrhythmic agent widely used in the management of various chronic disorders of cardiac rhythm. Unfortunately, the drug has a narrow therapeutic index, which clinically means that life-threatening arrhythmias are uncontrolled at subtherapeutic concentrations and severe toxicities manifest at only 2 to 3 times the minimum effective concentration.[9] Quinidine is metabolized by the liver to (3S)-3-hydroxyquinidine, 2′-oxoquinidinone, O-desmethylquinidine, and a metabolite tentatively identified as a rearrangement of quinidine-N-oxide.[10] The relative contribution of each biotransformation pathway to the overall removal of quinidine by drug metabolism is not yet known. The 3-hydroxyquinidine and 2′-oxoquinidinone metabolites have been shown to possess antiarrhythmic potencies comparable to those of the parent compound.[11] Less than 10 to 25% of a given quinidine dose is excreted unchanged.

As quinidine is largely eliminated by hepatic biotransformation, it is potentially subject to interventions that alter liver metabolic activity. Phenobarbital, phenytoin, and rifampin, all potent enzyme inducers, have been shown to at least double the rate of elimination of quinidine.[12,13] To date, no drug has been shown to decrease the clearance of quinidine by metabolic inhibition. However, pathophysiologic changes associated with congestive heart failure, such as reduced blood flow, have resulted in reduced quinidine clearance[14] and increased toxicity.[15]

In view of the implications of quinidine toxicity, it appeared reasonable to establish whether a significant drug interaction exists between quinidine and cimetidine.

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Methods

Six healthy male volunteers (aged 25 to 38 years) consented in writing to participate in the study, which was approved by the University and Institutional Review Committees. Volunteers were screened for normal health by medical history, physical examination (including prestudy electrocardiograms), and clinical laboratory testing (complete blood count with differential, platelet count, serum electrolytes, total bilirubin, alkaline phosphatase, serum transaminases, lactic dehydrogenase, glucose, total protein, blood urea nitrogen, serum creatinine, and urinalysis). Volunteers were nonsmokers and social users or nonusers of alcohol, with no known hypersensitivity to cimetidine or quinidine. They were asked to abstain from drinking alcoholic beverages during the course of the study.

The volunteers fasted for 8 hours before and 3 hours after quinidine administration. On the first day of the study, an oral dose of 400 mg quinidine sulfate (as two 200 mg tablets) was administered to each volunteer with approximately 100 ml of water. This dose is equivalent to about 330 mg of quinidine base. A total of 15 blood samples (5 ml each) were obtained at 0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration. A continuous intravenous drip with 5% dextrose solution was used to keep the forearm angiocath patent. Blood samples were collected in screw-top glass vials; the plasma was separated within 2 hours and stored at −20°C until assayed (Syva-Emit®). On the third day, the volunteers began a 7-day course of oral cimetidine, 300 mg 4 times daily. On the eighth day, a second 400 mg quinidine sulfate dose was administered and blood collections obtained as per day 1. Complete 48-hour urine collections were obtained after quinidine administration and the pH was determined. Urine aliquots were assayed for quinidine by high-pressure liquid chromatography.[16]

Plasma protein binding of quinidine was determined by equilibrium dialysis of plasma from quinidine-free volunteers against a 0.143 M phosphate buffer, titrated to pH 7.4, containing 1.25 μg/ml of H^3-quinidine (purified to >98% by thin-layer chromatography) (New England Nuclear, Boston, Massachusetts). In vitro binding of H^3-quinidine was measured in plasma samples obtained before and after a 5-day course of cimetidine. Plasma $alpha_1$-acid glycoprotein concentrations were measured on both study days by radial immunodiffusion (Calbiochem-Behring, La Jolla, California).

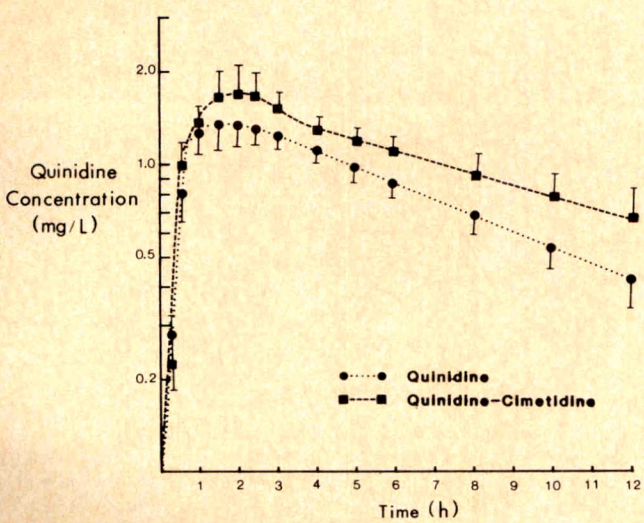

FIGURE 1. Plasma quinidine concentration-time profiles for mean (± standard error of the mean) data obtained after oral doses of 400 mg of quinidine sulfate in 6 normal volunteers with (**squares**) and without (**circles**) cimetidine treatment, 1.2 g daily for 7 days.

TABLE I Effect of Cimetidine on the Pharmacokinetics of Quinidine in 6 Normal Volunteers

	Without Cimetidine	With Cimetidine
Apparent oral clearance (liters/h)	25.5 ± 2.7	16.2 ± 1.4*
Elimination half-life (hours)	5.8 ± 0.2	9.0 ± 0.6*
Peak concentration (mg/liter)	1.5 ± 0.2	1.8 ± 0.2*
Time to peak (minutes)	91 ± 17	121 ± 15*
Unbound in plasma (%)	15.1 ± 0.7	15.1 ± 0.6
$Alpha_1$-acid glycoprotein (mg/dl)	74 ± 5	75 ± 4
Urinary excretion (%)	22.1 ± 1.6	22.4 ± 2.3

Values are expressed as means ± standard error of the mean.
* Significantly different ($p < 0.05$) from quinidine alone.

The electrocardiogram was monitored before and continuously after quinidine administration. Holter recordings were marked at all blood collection time points. During both control and study periods, QRS, R-R, and Q-T intervals were measured by a cardiologist blinded to the coded recordings. Interval values represent the average measurement of 5 sequential QRS complexes. The Q-T interval was corrected for heart rate (Q-Tc) according to the formula Q-Tc = Q-T measured/$\sqrt{\text{R-R}}$.[17] Blood pressures were obtained frequently during the first 4 hours and at 2 time points thereafter. Volunteers were asked to report any subjective effects (for example, dizziness, diarrhea, headache) felt to be associated with administration of quinidine or cimetidine.

The area under the plasma concentration-time curve after oral administration (AUC_o) of quinidine was extrapolated to infinity using the model-independent computer program LAGRAN. This program determines the areas and moments of plasma concentration-time data using the Lagrange technique[18] alone or in conjunction with linear or log-trapezoidal methods. The apparent oral clearance (Cl_o) was estimated using the formula Cl_o = dose/AUC_o. Since sampling around the peak was frequent, the highest value in the plasma concentration profile was used to represent the peak concentration (C_{max}). The time to reach this peak concentration was denoted T_{max}. Whereas AUC_o, Cl_o, C_{max}, and T_{max} were estimated essentially by model-independent means, the half-life was determined by nonlinear regression of the terminal phase of the plasma concentration-time profile.

The area under the electrocardiographic parameter change (such as ΔQ-Tc, ΔQRS) versus time curve was calculated for each volunteer from 0 to 12 hours by the linear trapezoidal method. Concentration-response profiles for quinidine, with and without cimetidine, were obtained by plotting the mean area under the change in Q-Tc versus time curve (ΔQ-Tc AUC) against the area under the plasma quinidine concentration-time curve (concentration AUC) as integrated for each blood collection interval.

Statistical comparisons were made using the paired Student's *t* test and linear regression analysis. The minimal level of significance was defined as $p < 0.05$.

Results

The mean quinidine plasma concentration-time profiles, with and without cimetidine treatment, are illustrated in Figure 1. After cimetidine treatment, statistically significant increases in quinidine elimination half-life of 55% (range 30 to 109), C_{max} of 21% (range 8 to 61), and T_{max} of 33% (range 8 to 118) were observed.

For each subject, the area under the oral quinidine plasma concentration-time profile was greater after treatment with cimetidine. This resulted in a decrease in mean Cl_o of 37% (range 23 to 49) from 25.5 ± 2.7 to 16.2 ± 1.4 liters/h ($p < 0.05$). The plasma protein binding of quinidine, plasma alpha$_1$-acid glycoprotein concentrations, and the percent urinary recovery of unchanged quinidine were unaffected by cimetidine treatment. These data are listed in Table I.

The alterations in pharmacokinetic variables were accompanied by increases in pharmacodynamic responses, although these differences failed to achieve statistical significance. The mean changes (± standard error of the mean) in Q-Tc after oral quinidine administration with and without cimetidine, are shown in Figure 2. Without cimetidine, the mean area under the Q-Tc change versus time curve (ΔQ-Tc area) was 576 ± 101 ms·h, demonstrating a notable prolongation of the rate-corrected Q-T time after a single oral quinidine dose. With cimetidine treatment, the mean ΔQ-Tc area increased 28% to 727 ± 78 ms·h. Similarly, the mean ΔQ-T area increased 51% from 362 ± 56 to 545 ± 71 ms·h, the mean R-R area was 9,443 ± 378 ms·h before and 9,335 ± 370 ms·h after cimetidine therapy, and the mean ΔQRS area was 40 ± 10 ms·h before and 37 ± 12 ms·h with the addition of cimetidine.

A pooled concentration-response curve for quinidine, with and without cimetidine, is illustrated in Figure 3. A strong relationship between quinidine plasma concentration AUC and ΔQ-Tc AUC was observed with ($r = 0.989$) and without cimetidine ($r = 0.965$). Cimetidine treatment did not shift the concentration-response profile of quinidine, as the slopes (65.9 ± 3.0 versus 62.3 ± 5.1, ms·liter/mg) and intercepts (−5.4 ± 3.3 versus −4.6 ± 4.5 ms·h) with and without cimetidine, respectively, were not statistically different. However, after cimetidine treatment, higher plasma quinidine concentrations were achieved with equivalent quinidine dosage. This resulted in predictable increases in ΔQ-Tc.

All volunteers had a transient decrease in mean blood pressure (10 to 30 mm Hg), 2 volunteers had diarrhea from quinidine, and 1 subject had headaches while taking cimetidine.

Discussion

When a drug with a low hepatic extraction (for example, Cl_o <6 liters/h) is administered either intravenously or orally, elimination depends mainly upon intrinsic hepatic clearance. The inhibition of low clearance drugs by cimetidine has been previously described for warfarin,[4] diazepam,[5] theophylline,[6] and phenytoin.[7] Low clearance drugs are relatively insensitive to changes in hepatic blood flow, whereas high clearance drugs (for example, Cl_o >240 liters/h) are perfusion rate-dependent. Alterations in hepatic metabolism influence high clearance drugs after oral administration (first-pass effect), but not after intravenous administration. However, cimetidine has been demonstrated to decrease the clearance of intravenously administered high

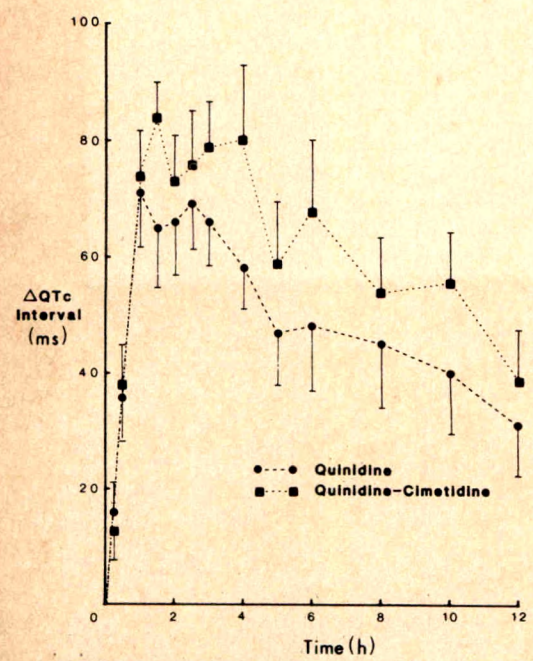

FIGURE 2. Effect of cimetidine on the pharmacodynamics of quinidine. Values represent the mean (± standard error of the mean) change in rate-corrected Q-T time obtained after a single oral dose of 400 mg quinidine sulfate in 6 normal volunteers with **(squares)** and without **(circles)** cimetidine treatment, 1.2 g daily for 7 days.

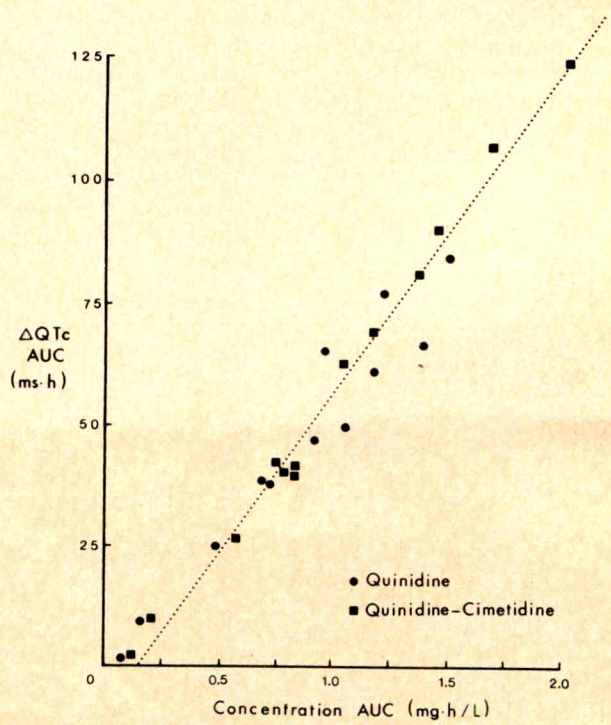

FIGURE 3. Effect of cimetidine on the concentration-response curve of quinidine. Values represent the mean data for area under the change in Q-Tc versus time curve (ΔQ-Tc AUC) as plotted against the area under the plasma quinidine concentration-time curve (concentration AUC) integrated between each blood collection time point. A strong correlation between concentration and response was observed with **(squares)** ($r = 0.989$) and without **(circles)** ($r = 0.965$) cimetidine treatment. Slopes and intercepts remained unchanged after cimetidine treatment (see text).

clearance drugs such as propranolol[3] and lidocaine.[8] This effect may be partially explained by cimetidine-induced reduction in hepatic blood flow.[3] In the case of lidocaine, a reduction in volume of distribution was observed.[8]

The mean apparent oral clearance of quinidine was 25.5 liters/h in our normal volunteers. Although quinidine is a relatively low extraction drug, factors that alter hepatic perfusion cannot be totally ignored. The higher peak concentrations of quinidine and the delay in the time to achieve these peak concentrations after cimetidine treatment may be related to hepatic enzyme inhibition, reduced liver blood flow, or both. Furthermore, an increase in quinidine absorption in the presence of cimetidine cannot be excluded as a possible explanation for the observed elevations in quinidine plasma concentrations.

Regardless of the specific pharmacokinetic mechanisms involved, elevations in plasma quinidine concentrations are presumably associated with corresponding increases in myocardial tissue concentrations at steady state. Clinically, this is reflected in changes in electrocardiographic parameters which are known to be sensitive indicators of quinidine activity.[19] In our study, there was an observed increase in mean area under the Q-T and Q-Tc change versus time curves of 50 and 28%, respectively, after coadministration of cimetidine and quinidine. This suggests that alterations in quinidine pharmacokinetics by cimetidine are mirrored by changes in quinidine pharmacodynamics. The concentration-response curve for quinidine was unchanged in the presence of cimetidine (Fig. 3). This implies the observed increases in the pharmacodynamic effects of quinidine were the result of increased plasma quinidine concentrations and not due to any direct effect of cimetidine or its metabolites on the myocardium.

Cimetidine alters the disposition of oral quinidine in normal volunteers. Although multiple dose studies in patients are desirable, it is not unreasonable to postulate that similar changes may occur in patients stabilized on chronic oral quinidine when cimetidine therapy is initiated. This drug interaction may also predispose patients to the proarrhythmic effects of quinidine. Malignant arrhythmias such as ventricular tachycardia and fibrillation have been observed in quinidine-treated patients after marked Q-T prolongation.[20] In view of the existing potential for enhanced pharmacologic activity, these patients may require initial observation for early signs of quinidine toxicity as monitored by quinidine levels, frequent electrocardiographic monitoring, and clinical assessment.

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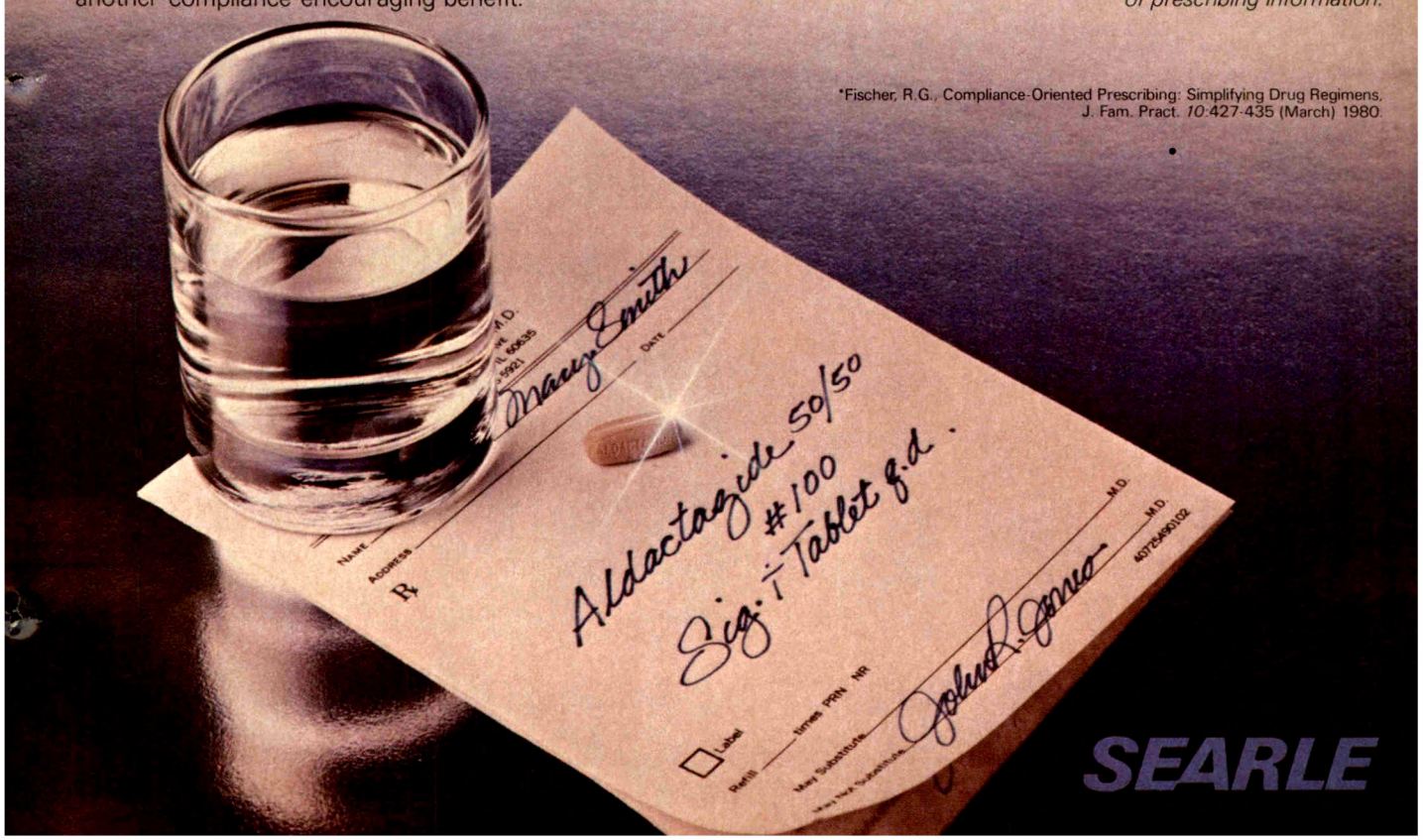

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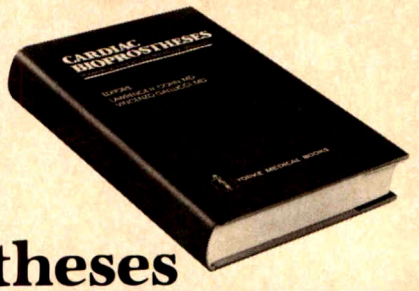

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

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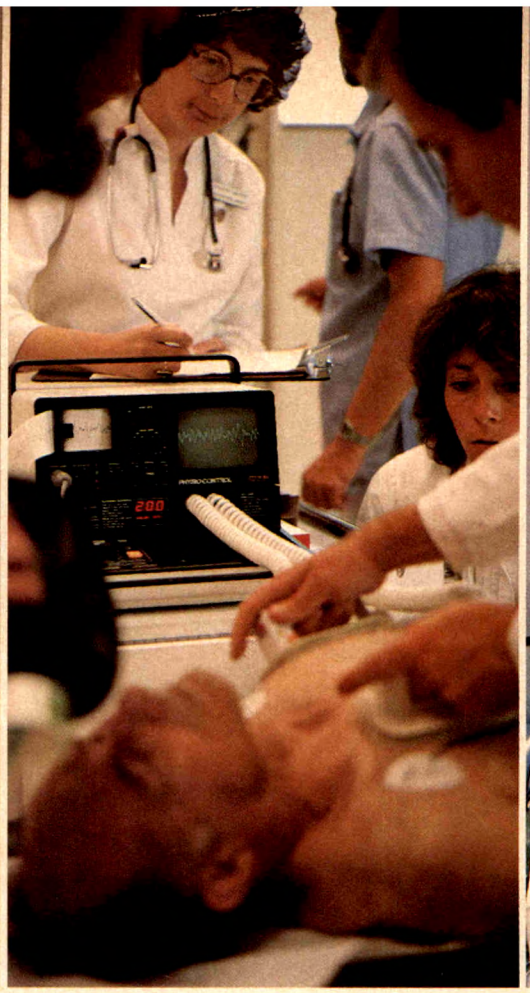

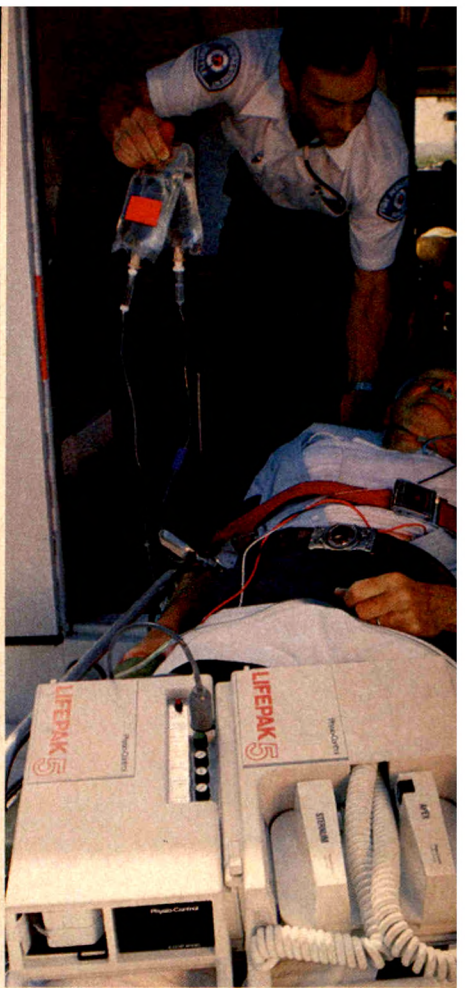

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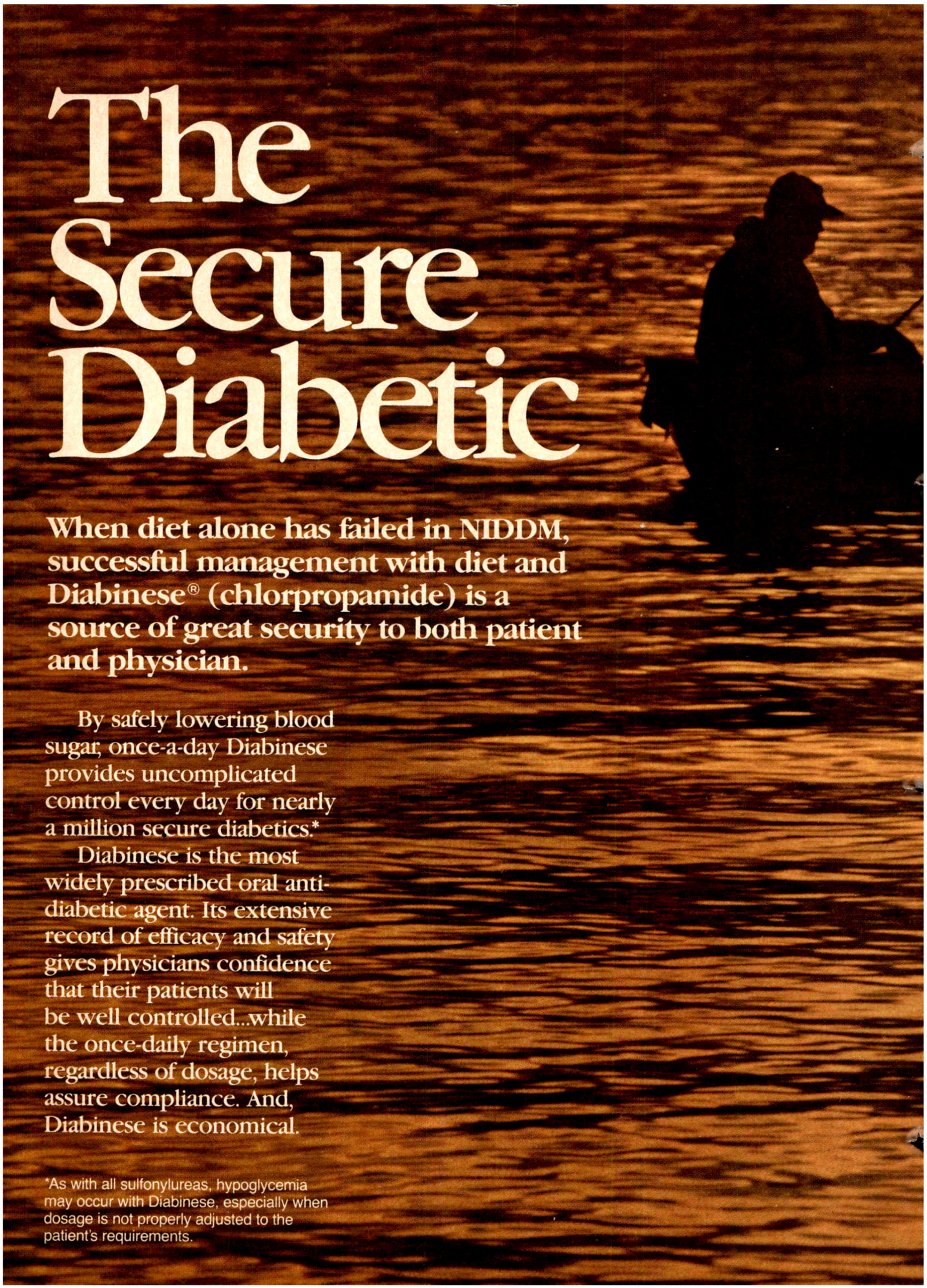
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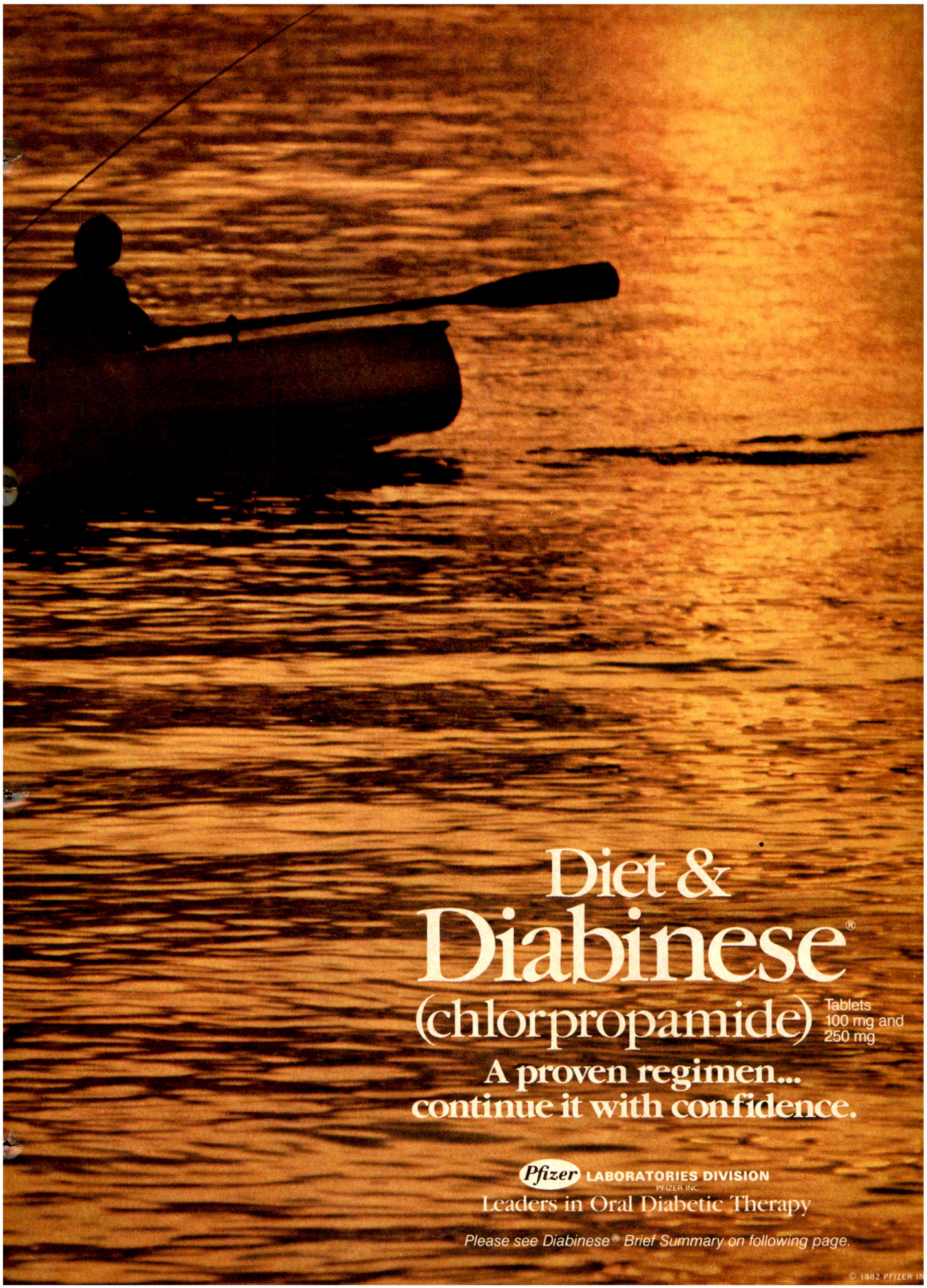
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Please see Diabinese® Brief Summary on following page.
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Tablets 100 mg and 250 mg

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Diabinese is contraindicated in patients with serious impairment of hepatic, renal, or thyroid function.
Precautions: Use chlorpropamide with caution with barbiturates, in patients with Addison's disease or in those ingesting: alcohol, antibacterial sulfonamides, thiazides, phenylbutazone, salicylates, probenecid, dicoumarol or MAO inhibitors. Adequate dietary intake should be assured in all patients using Diabinese.
Warnings: DIABINESE (CHLORPROPAMIDE) SHOULD NOT BE USED IN JUVENILE DIABETES OR IN DIABETES COMPLICATED BY ACIDOSIS, COMA, SEVERE INFECTION, MAJOR SURGICAL PROCEDURES, SEVERE TRAUMA, SEVERE DIARRHEA, NAUSEA AND VOMITING, ETC. HERE, INSULIN IS INDISPENSABLE.
HYPOGLYCEMIA, IF IT OCCURS, MAY BE PROLONGED. (SEE ADVERSE REACTIONS.) IN INSTANCES OF CONCOMITANT USE WITH INSULIN, PATIENTS SHOULD BE CAREFULLY MONITORED.
Adverse Reactions: Usually dose-related and generally respond to reduction or withdrawal of therapy. Generally transient and not of a serious nature and include anorexia, nausea, vomiting and gastrointestinal intolerance; weakness and paresthesias.
Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occasionally occurred, including jaundice, skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood. They occur characteristically during the first six weeks of therapy. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug. The more severe manifestations may require other therapeutic measures, including corticosteroid therapy. Diabinese should be discontinued promptly when the development of sensitivity is suspected.
Jaundice has been reported, and is usually promptly reversible on discontinuance of therapy. THE OCCURRENCE OF PROGRESSIVE ALKALINE PHOSPHATASE ELEVATION SHOULD SUGGEST THE POSSIBILITY OF INCIPIENT JAUNDICE AND CONSTITUTES AN INDICATION FOR WITHDRAWAL OF THE DRUG.
Leukopenia, thrombocytopenia and mild anemia, which occur occasionally, are generally benign and revert to normal, following cessation of the drug.
Cases of aplastic anemia and agranulocytosis, generally similar to blood dyscrasias associated with other sulfonylureas, have been reported.
BECAUSE OF THE PROLONGED HYPOGLYCEMIC ACTION OF DIABINESE, PATIENTS WHO BECOME HYPOGLYCEMIC DURING THERAPY WITH THIS DRUG REQUIRE CLOSE SUPERVISION FOR A MINIMUM PERIOD OF 3 TO 5 DAYS, during which time frequent feedings or glucose administration are essential. The anorectic patient or the profoundly hypoglycemic patient should be hospitalized.
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Edema associated with hyponatremia has been infrequently reported. It is usually readily reversible when medication is discontinued.
Dosage: The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally, cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED. The mild to moderately severe, middle-aged, stable diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on smaller amounts of Diabinese, in the range of 100 to 125 mg daily.
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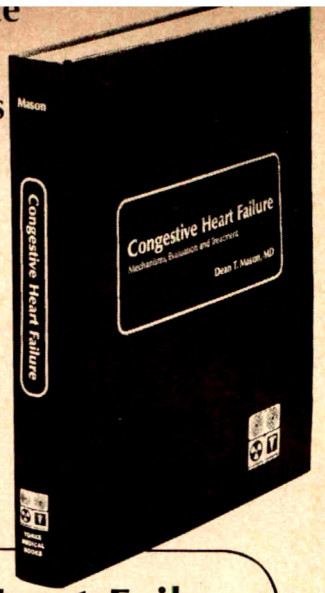

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Dean T. Mason, M.D.

This rare treatment of such a multifaceted subject provides an unusual opportunity for the busy clinician to add to his knowledge in a minimum amount of time. Any area of immediate interest can be rapidly located and as much data as needed can be quickly extracted. The concentration on improved clinical management will be appreciated by every internist, cardiologist, generalist, and any professional involved in cardiovascular medicine.

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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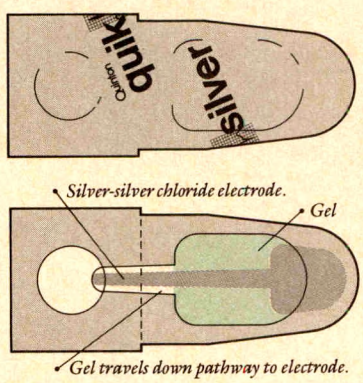

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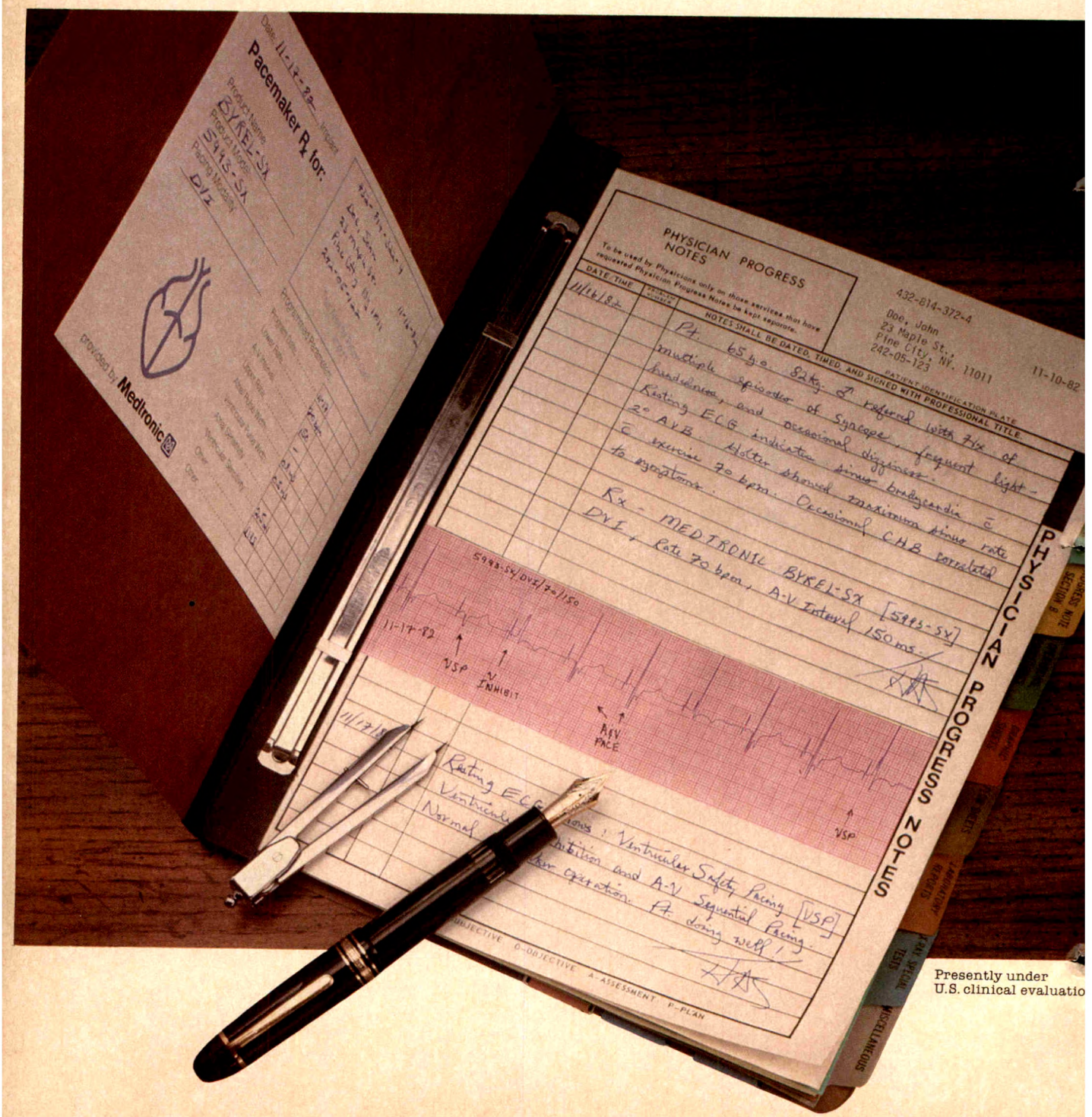

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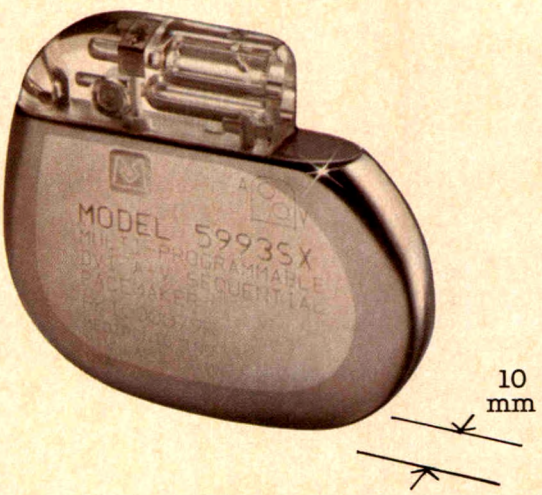

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Byrel-SX Model 5993-SX
Programmable Parameters

Rate	DVI	VVI
	40-120 bpm	40-130 bpm
A-V Internal	25-250 ms	NA
Atrial Pulse Width	0.05, 0.1, 0.2...1.5 ms	NA
Ventricular Pulse Width	0.05, 0.1, 0.2...1.5 ms	0.05, 0.1, 0.2...1.5 ms
Ventricular Sensitivity	2.5, 5.0 mv Asynchronous	2.5, 5.0 mv Asynchronous

Power Source Depletion Characteristics

Initial Stage

Mode	as programmed
Voltage	2.2 V
Magnet rate	75 bpm

Secondary Stage

Mode	VVI at 65 bpm
Voltage	2.0 V

INTENDED USE

The Model 5993-SX universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

In the A-V sequential (DVI) mode, the Model 5993-SX has application in the following:

Sick Sinus Syndrome (sinus brady-cardia, sinus arrest, S-A block, and the brady-tachy syndrome).

A-V nodal reentrant tachycardias. (Short A-V interval settings may be useful in controlling reentrant tachy-cardias.)

Atrial and ventricular ectopic arrhythmias.

At any time, the Model 5993-SX can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 5993-SX A-V pulse generator is under clinical investigation. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Use" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 5993-SX pulse generator during its clinical investigation. Patients should be advised that the Model 5993-SX generator is under clinical investigation.

CONTRAINDICATIONS

There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician. In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation of flutter.

WARNINGS

Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site. Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

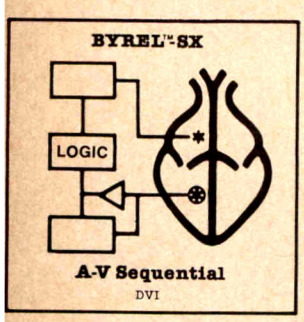
Positioning a magnet or the programmer over the pulse generator makes it subject to programming. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programmer has been positioned over the pulse generator.

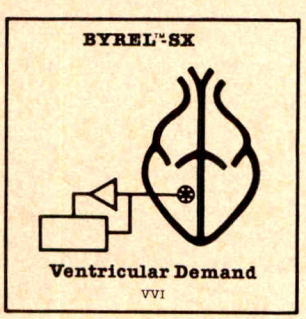
PRECAUTIONS

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

SIDE EFFECTS

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.





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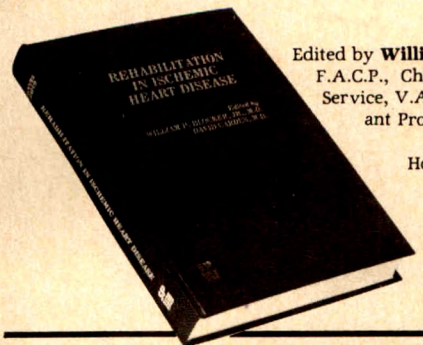

Edited by **William P. Blocker, Jr., M.D.,** F.A.C.P., Chief, Rehabilitation Medicine Service, V.A. Hospital, Houston, Assistant Professor of Physical Medicine, Baylor College of Medicine, Houston, and **David Cardus**, M.D., F.A.C.C., Professor of Physiology and Rehabilitation, Baylor College of Medicine, Houston, Texas.

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Approx. 500 pp., 188 figs. & tbls., large format 8½x11, 1982, $80.00

CONTENTS

PREFACE
PART I. EPIDEMIOLOGICAL ASPECTS
PART II. PATHOGENIC ASPECTS
PART III. CLINICAL ASPECTS
PART IV. EVALUATIVE ASPECTS
PART V. MANAGEMENT ASPECTS
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NITROSTAT®
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Before prescribing, please see full prescribing information. A Brief Summary follows:

INDICATIONS
Nitroglycerin is indicated for the prophylaxis, treatment and management of patients with angina pectoris.

CONTRAINDICATIONS
Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS
Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS
Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION
One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

HOW SUPPLIED
Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.

0.15 mg (1/400 grain):
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*Five-year expiration date when stored at recommended storage conditions in an unopened bottle. Data on file, Medical Affairs Dept. Parke-Davis.

REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

Please see preceding page for brief summary of prescribing information.

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PD-58-JA-1408-P-1(12-82)

Relation Between Functional Response to Nitroglycerin and Extent of Myocardial Necrosis in Dogs: Mapping of the Left Ventricle by 2-Dimensional Echocardiography

KEICHO SHIMOURA, MD, SAMUEL MEERBAUM, PhD, TATSUO SAKAMAKI, MD, SHUJI KONDO, MD, MICHAEL C. FISHBEIN, MD, JACOB Y-RIT, MD, CHUWA TEI, MD, PRAVIN M. SHAH, MD, and ELIOT CORDAY, MD

The relation between functional response to brief nitroglycerin infusions and extent of myocardial damage was studied sequentially in closed-chest dogs with acute occlusion of the left anterior descending coronary artery. Two-dimensional echocardiography was used to derive segmental left ventricular (LV) function (systolic fractional area change and systolic wall thickening), and this function was compared with the extent of necrosis measured 5 hours after occlusion in equivalent segments of corresponding pathologic slabs. Two-dimensional echocardiographic study before the dogs were killed indicated that remote nonnecrotic segments always responded to nitroglycerin by significant augmentation of segmental LV function. Segments in which necrosis was <40% showed a significant nitroglycerin-induced potentiation in segmental LV function. In contrast, segments in which necrosis was >60% had no potentiation with nitroglycerin. In those segments in which eventual necrosis was 60 to 80%, significant nitroglycerin-induced augmentation in segmental LV function was observed only before and 30 minutes after the coronary occlusion. When the degree of necrosis was >80%, no significant potentiation of segmental LV function was observed even as early as 30 minutes after occlusion. Thus, the degree of nitroglycerin-induced potentiation of segmental cardiac function is closely associated with the extent of myocardial necrosis in the particular ventricular segment. Two-dimensional echocardiography coupled with a nitroglycerin potentiation test might be useful for assessment of the viability of ischemic myocardium.

Nitroglycerin administration is known to be associated with systemic effects on both afterload and preload, and also alters the distribution of myocardial blood flow.[1–10] In addition to its application for treatment, nitroglycerin has frequently been used in patients with ischemic heart disease to elicit a response that might characterize functional viability, such as improvement of abnormal wall motion in asynergic ischemic segments.[11–18] Nitroglycerin-induced reversal of regional wall motion abnormalities generally correlated well with and was often predictive of salvage of corresponding regions after subsequent bypass revascularization surgery.[15] However, few systematic data have been reported on the relation between the underlying pathologic characteristics of ischemic asynergic left ventricular (LV) regions[19,20] and their response during brief nitroglycerin interventions.

In this study, we examined and correlated in closed-chest dogs the extent of myocardial necrosis in LV segments in relation to their functional response to nitroglycerin as defined by 2-dimensional (2-D) echocardiography. We also studied the time course of the segmental functional response to brief nitroglycerin interventions during coronary artery occlusions, and related the progressive changes in response to eventual myocardial segment histopathology.

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TABLE I Effects of Nitroglycerin (NTG) on Hemodynamic Variables

	MAP (mm Hg)			HR (beats/min)			LV dP/dt (mm Hg/s)		
	Pre-NTG	NTG	% Change	Pre-NTG	NTG	% Change	Pre-NTG	NTG	% Change
				Before Occlusion					
	101.3 ±7.9	93.6 ±9.1†	−7.7 ±3.2	78.3 ±13.5	106.5 ±17.5†	37.5 ±20.7	1884 ±236	2197 ±175†	17.3 ±10.4
				After Occlusion					
30 min	112.0 ±15.3	101.7 ±12.3†	−9.0 +2.1	106.9 ±15.7	130.2 +16.3†	22.9 ±15.6	1639 +255	1939 ±395†	18.2 ±12.6
1 hour	113.8 ±10.0	104.3 ±8.9†	−8.3 ±1.3	113.6 ±14.8	131.4 ±13.1†	16.8 ±14.5	1720 ±361	1940 ±358†	13.6 ±9.5
2 hours	119.4 +15.0	108.5 ±12.1†	−8.9 ±3.1	108.2 ±18.0	125.9 +26.0*	16.8 ±18.6	1600 +362	1889 ±473†	18.2 ±11.1
3 hours	119.8 ±11.6	107.6 ±10.9†	−10.1 ±4.3	106.8 ±16.1	124.4 ±19.0†	16.8 ±9.8	1514 ±364	1733 ±420†	14.7 ±8.8
5 hours	113.9 ±15.0	102.5 ±13.6†	−9.9 ±1.9	115.9 ±24.9	131.3 ±35.6*	12.5 ±10.5	1455 ±238	1620 ±393*	10.7 +11.3

Values are means ± standard deviation.
* $p < 0.05$ versus before NTG.
† $p < 0.005$ versus before NTG.

Methods

Experimental procedures: Ten mongrel dogs, weighing 21 to 36 kg, were anesthetized intramuscularly with morphine (2 mg/kg) and intravenously with sodium pentobarbital (30 mg/kg). The dogs were respirated with a Harvard ventilator through a cuffed endotracheal tube. Echocardiographic studies and all catheter placements were performed in the closed-chest preparation. A 7Fr catheter was placed into the ascending aorta and a 7Fr pigtail catheter into the left ventricle. Aortic and LV blood pressures were recorded using Statham P23Db transducers. LV dP/dt was derived by means of resistance-capacitance differentiation. A 7Fr Swan-Ganz thermodilution balloon-tipped catheter was inserted into the pulmonary artery and connected to an Edwards cardiac output computer 9520 for cardiac output measurements. Pressures, LV dP/dt (first differential of LV pressure), and a precordial electrocardiogram were monitored simultaneously on an Electronics for Medicine recorder at a paper speed of 25 or 50 mm/s.

The left anterior descending coronary artery (LAD) was occluded in the closed-chest dogs with a 2 or 3Fr intracoronary balloon catheter at a site just beyond the first diagonal branch. Before coronary occlusion and 30, 60, 120, 180, and 300 minutes after LAD occlusion, a set of control (prenitroglycerin) measurements were obtained, including 2-D echocardiography, cardiac output, blood pressures, and the electrocardiogram. After individual control measurements were recorded, a nitroglycerin test was performed by intravenously administering nitroglycerin through a femoral vein catheter using a Harvard infusion pump. The infusion of nitroglycerin was controlled in a manner to cause a decrease in mean aortic pressure of approximately 10% from the respective prenitroglycerin control state (average nitroglycerin dose 3 μg/kg/min, range 1 to 6). After the aortic pressure had reached a steady state at the desired level, nitroglycerin infusion was maintained for 5 minutes, during which time the aforementioned set of recordings was repeated. Nitroglycerin was then discontinued until the next nitroglycerin test. The total period of individual nitroglycerin tests, performed before and after coronary occlusion, did not exceed 10 minutes. After 5 hours of LAD occlusion and a final set of control as well as nitroglycerin measurements, the dogs were killed and pathologic studies were performed, including delineation of myocardial necrosis in ventricular slabs.

Two-dimensional echocardiographic examination: A mechanical ultrasonic sector scanner (ATL Mark III, Advanced Technology Laboratories, Bellevue, Washington) was used to perform the 2-D echocardiographic studies. Echocardiographic examination of the heart was performed in closed-chest dogs according to methods previously detailed by our laboratory.[21–23]

Regional LV wall motion analysis of short-axis LV sections in individual beats was performed in a standardized manner. The geographic center of the epicardial outline and the junction between the anterior right ventricle and ventricular septum were used as internal reference points, defining an indexing line for standardized computer-aided (PDP 11/34 minicomputer) division of each cross section into eight 45° segments. In correcting for translation and rotation, a floating reference system of analysis was used in which the epicardial geographic centers and indexing lines of both end-diastolic and end-systolic outlines of individual beats were superimposed. Individual segmental systolic fractional area changes and systolic wall thickening were computed as indexes of myocardial contraction: percent systolic fractional area change (FAC%) = [(EDLA − ESLA)/EDLA] ×100; percent systolic wall thickening (WT%) = [(ESWT − EDWT)/EDWT] ×100, where EDLA = end-diastolic luminal area, ESLA = end-systolic luminal area, EDWT = end-diastolic wall thickness, ESWT = end-systolic wall thickness, and wall thickness = 2 × muscle area/(epicardial perimeter + endocardial perimeter).

Morphologic analysis: The dogs' hearts were excised and sectioned transversely into 5 slabs, each approximately 10 mm thick, parallel to the atrioventricular groove. Each slice was then incubated in triphenyltetrazolium chloride[24,25] and fixed in formalin for subsequent processing. The extent and the site of the necrosis were confirmed by histologic examination.[24,25] The triphenyltetrazolium-chloride–delineated areas of necrosis were compared with extent of asynergy and regional response to nitroglycerin, measured in 2-D echocardiographic LV sections corresponding to carefully matched equivalent anatomic slabs. This matching was performed using every structural landmark in both 2-D echocardiographic LV sections and anatomic slabs.

TABLE I, continued

	LVEDP (mm Hg)			CO (liters/min)			SV (ml/min)		
	Pre-NTG	NTG	% Change	Pre-NTG	NTG	% Change	Pre-NTG	NTG	% Change
				Before Occlusion					
	2.8 ±1.4	0.3 ±0.7†	−80.0 ±35.0	2.2 ±0.6	2.7 ±0.7†	23.5 ±18.8	29.1 ±9.3	26.4 ±9.2	−8.3 ±19.2
				After Occlusion					
30 min	9.2 ±6.2	3.0 ±3.3†	−71.7 ±19.7	2.5 ±0.8	2.8 ±0.8*	10.9 ±12.7	24.1 ±8.0	21.4 ±5.9*	−9.2 ±9.7
1 hour	8.8 ±5.6	4.5 ±4.4†	−58.5 ±29.3	2.5 ±0.8	2.5 ±0.7	3.7 ±18.2	21.9 ±6.4	19.2 ±5.2*	−11.2 ±12.1
2 hours	11.7 ±6.3	5.5 ±4.7†	−63.4 ±24.6	2.1 ±0.6	2.1 ±0.5	2.7 ±24.3	19.9 ±6.5	17.1 ±5.1	−10.5 ±24.2
3 hours	11.1 ±5.5	5.3 ±3.6†	−58.5 ±26.3	1.9 ±0.5	2.1 ±0.4	13.6 ±17.5	17.8 ±6.3	17.1 ±4.6	−1.2 ±16.2
5 hours	9.9 ±5.1	5.4 ±3.2†	−50.4 ±20.7	2.1 ±0.5	2.1 ±0.3	0.7 ±16.8	18.3 ±3.6	16.2 ±3.1	−9.3 ±20.5

CO = cardiac output; HR = heart rate; LV dP/dt = first differential of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean aortic pressure; SV = stroke volume.

Data analysis: Two-dimensional echocardiographic measurements in segments of LV short-axis sections were expressed as systolic fractional area change and systolic wall thickening, and were always derived for periods before and during nitroglycerin at the different times after LAD occlusion. The 2-D echocardiographically derived data on cardiac function were correlated with the extent of equivalent anatomic slab necrosis, also expressed as a percentage of each slab segment, measured with planimetry.[25]

Statistical analysis was performed by Student's paired *t* test. P values <0.05 were considered statistically significant.

Reproducibility: To study reproducibility, 2-D echocardiographic analysis was performed both by 1 observer at different times (intraobserver) and independently by 2 observers (interobserver) in 10 short-axis 2-D echocardiographic views, 1 view from each dog. Intra- and interobserver reproducibility study of segmental percent necrosis measurements was performed in 1 slab from each dog. A linear regression analysis was performed and a mean percent error was calculated.

Results

Effects of nitroglycerin on hemodynamic function: The nitroglycerin-induced hemodynamic changes at different stages of the LAD occlusion are summarized in Table I. Although aortic pressures appeared slightly increased after the LAD occlusion, this change was not statistically significant. Individual nitroglycerin injections decreased mean aortic pressure by 9 ± 3% (mean ± standard deviation, range 8 to 10%) from respective prenitroglycerin levels. Initially, spontaneous heart rate increased significantly soon after the LAD occlusion, but the rate did not change further throughout the 5-hour experimental period. Before the LAD occlusion, nitroglycerin caused a significant increase in heart rate (38 ± 21%). A significant but smaller increase in heart rate was also evident in response to nitroglycerin after the LAD occlusion (17 ± 14%, range 13 to 23%). Maximal LV dP/dt increased significantly and LV end-diastolic pressure decreased significantly during nitroglycerin testing, both before and throughout the LAD occlusion. Cardiac output, measured with thermodilution, increased significantly as a result of nitroglycerin before and 30 minutes after LAD occlusion. However, there was no significant nitroglycerin-induced change in cardiac output after 1, 2, 3, and 5 hours of the LAD occlusion. Calculated LV stroke volume decreased successively after the LAD occlusion, and was further reduced during the individual nitroglycerin test periods.

TABLE II Reproducibility of Duplicate Measurements of 2-D Echocardiographic Segmental LV Function, and Segmental Percent Necrosis in Pathologic Slabs

	r	Slope	Intercept (%)	SEE	Mean Error (%)
			Intraobserver Reproducibility		
FAC%	0.92	0.97	1.41	3.82	7.7 ± 7.0
WT%	0.93	0.90	1.80	7.06	23.5 ± 18.8
% Necrosis	0.98	0.94	0.69	2.82	2.7 ± 2.1
			Interobserver Reproducibility		
FAC%	0.90	0.90	5.26	3.90	9.4 ± 8.7
WT%	0.93	0.87	3.55	6.69	26.4 ± 20.3
% Necrosis	0.99	0.94	2.08	2.85	2.8 ± 2.9

FAC% = systolic fractional area change; r = correlation coefficient; SEE = standard error of the estimate; WT% = systolic wall thickening.

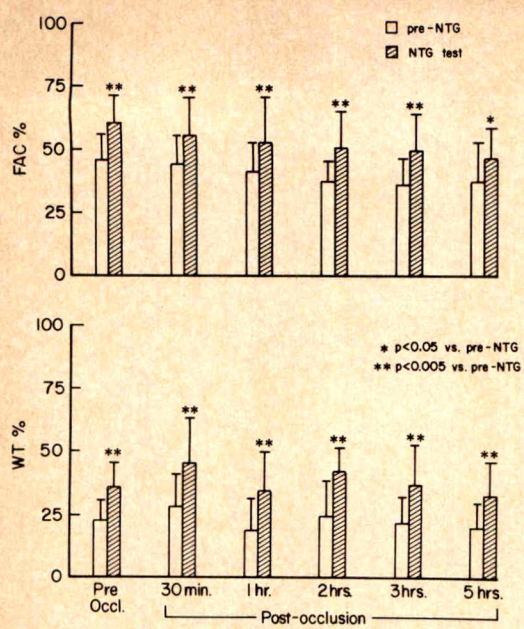

FIGURE 1. Alterations of 2-D echocardiographically derived segmental left ventricular function in a low papillary left ventricular cross section during nitroglycerin (NTG) tests performed before occlusion and up to 5 hours after left anterior descending artery occlusion (Occl.). Function was potentiated by nitroglycerin in all cardiac segments that were found to have no necrosis after 5 hours of left anterior descending artery occlusion. FAC % = systolic fractional area change; WT% = systolic wall thickening.

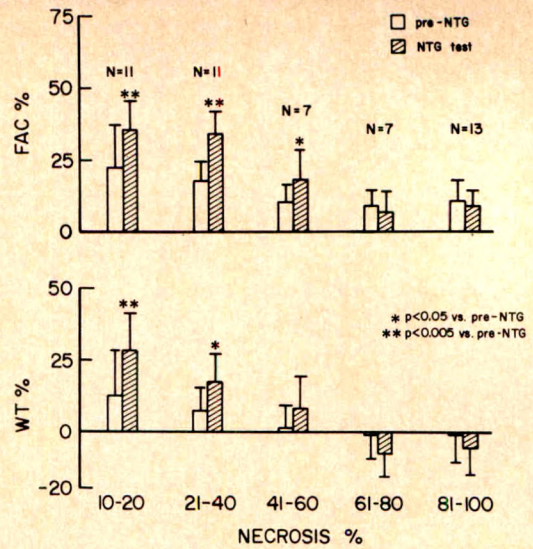

FIGURE 2. Relation between 2-D echocardiographically derived segmental functional response to nitroglycerin (NTG) just before death, and segmental extent of necrosis in equivalent left ventricular slabs 5 hours after left anterior descending artery occlusion. Necrotic involvement was delineated in slabs with triphenyltetrazolium chloride. FAC% = systolic fractional area change; WT% = systolic wall thickening.

Reproducibility: Data of linear regression analysis and mean percent errors are shown in Table II. Both intra- and interobserver reproducibility of segmental systolic fractional area change exhibited satisfactory correlation coefficients (r = 0.92, 0.90) and small mean percent errors (7.7, 9.4%), but mean percent errors of segmental systolic wall thickening were comparatively large (23.5, 26.4%), in spite of apparently adequate correlation coefficients (r = 0.93, 0.93). Reproducibility of segmental measurements of percent necrosis exhibited good correlation coefficients (r = 0.98, 0.99) and small mean percent errors (2.7, 2.8%).

Two-dimensional echocardiographic measurements: During nitroglycerin testing, LV ejection fraction, calculated from LV end-diastolic and end-systolic

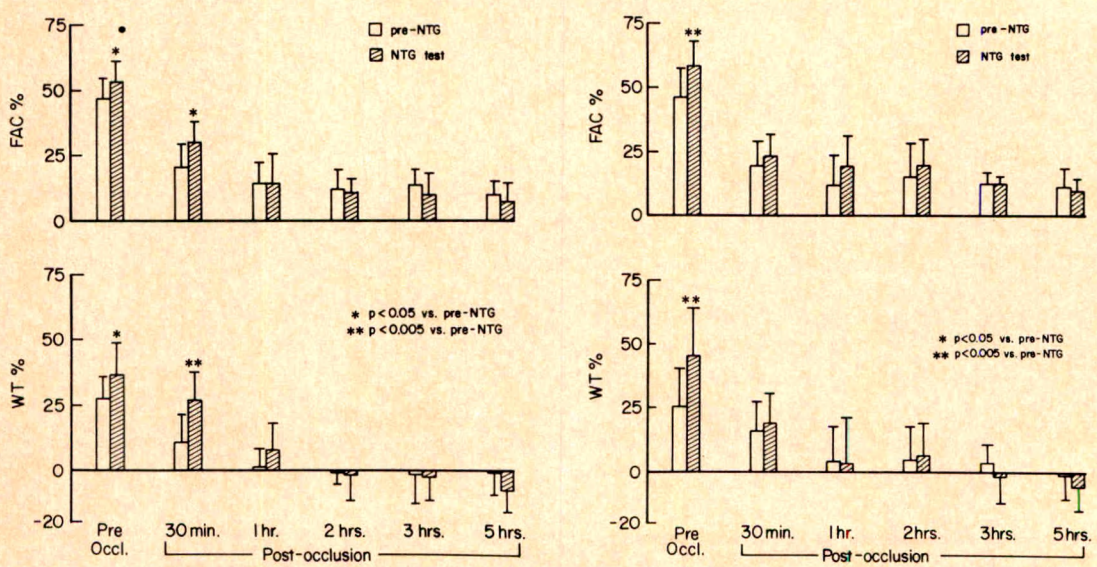

FIGURE 3. Left, time course of functional response to nitroglycerin of left ventricular segments in which the ultimate necrosis was between 61 and 80% after 5 hours of left anterior descending artery occlusion (Occl.). **Right,** time course of functional response to nitroglycerin of left ventricular segments in which the ultimate necrosis was >80% after 5 hours of left anterior descending artery occlusion. FAC% = systolic fractional area change; WT% = systolic wall thickening.

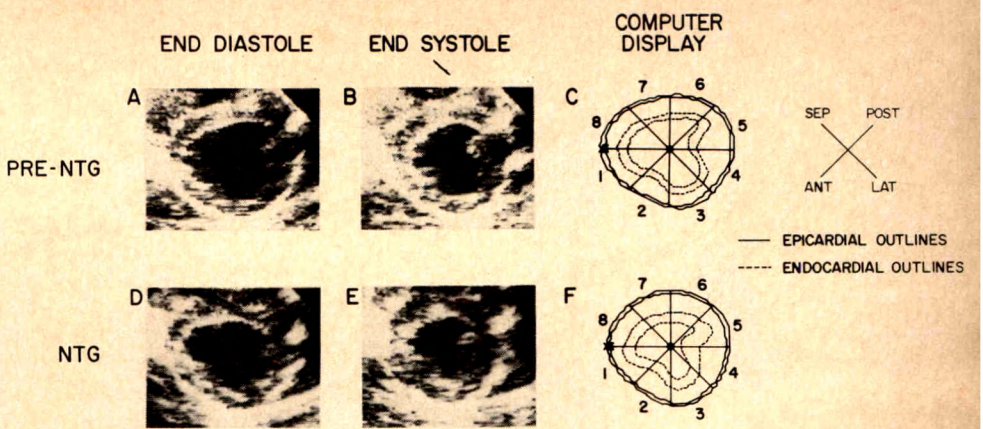

FIGURE 4. Two-dimensional echocardiographic images of left ventricular short-axis cross sections obtained at low papillary level before the left anterior descending artery occlusion. **A,** prenitroglycerin, end-diastolic image; **B,** prenitroglycerin, end-systolic image; **D,** end-diastolic image during nitroglycerin; **E,** end-systolic image during nitroglycerin; **C and F,** superimposed endocardial and epicardial outlines before and during nitroglycerin. Note that nitroglycerin-potentiated contraction was uniform throughout the section. ANT = anterior; LAT = lateral; NTG = nitroglycerin; POST = posterior; SEPT = septal.

volumes, increased significantly both before and throughout the LAD occlusion. After distal LAD occlusion, wall motion abnormalities observed with 2-D echocardiography were most distinct at the low papillary and near-apical LV levels. Hence, emphasis was placed on analyzing 2-D echocardiographic LV views in a short-axis low papillary level cross section.

Figure 1 shows 2-D echocardiographically derived data on segmental LV function (systolic fractional area change and systolic wall thickening) in remote nonischemic segments, whose site was corroborated by postmortem triphenyltetrazolium chloride staining of equivalent LV slabs. Significant augmentation of segmental LV function was observed in these remote segments during nitroglycerin testing at all times before and throughout the LAD occlusion.

Triphenyltetrazolium chloride staining of LV slabs after 5 hours of LAD occlusion indicated various extents of necrosis in different segments of the echo-delineated underperfused jeopardized LV zone. Figure 2 shows the relation between segmental extent of necrosis noted 5 hours after the LAD occlusion and 2-D echocardiographically derived segmental LV function measured just before death, both before and during the nitroglycerin test. In those segments in which the ultimate necrosis was <40%, a significant potentiation in segmental LV function was noted during nitroglycerin testing at 5 hours after the LAD occlusion. In segments where the

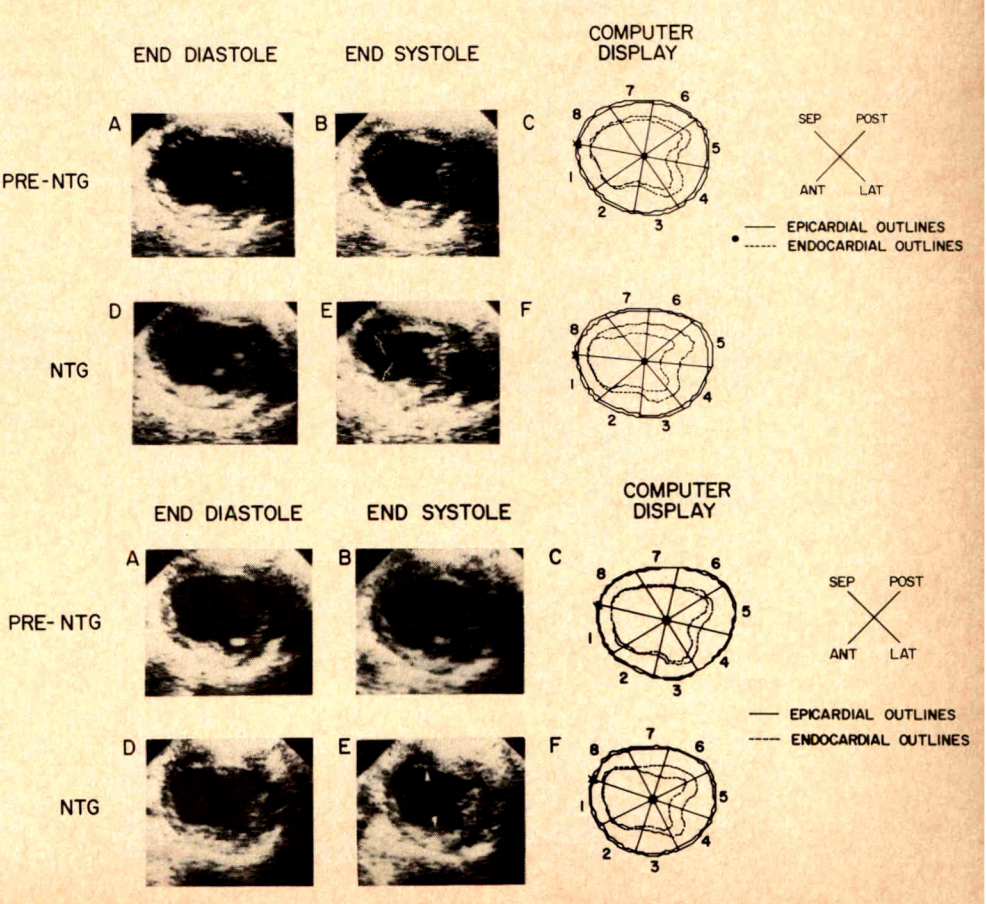

FIGURE 5. Two-dimensional echocardiographic images of left ventricular short-axis cross sections at a low papillary level, obtained 30 minutes (**top**) and 5 hours (**bottom**) after LAD coronary occlusion. **A,** prenitroglycerin, end-diastolic image; **B,** prenitroglycerin, end-systolic image; **D,** end-diastolic image during nitroglycerin test; **E,** end-systolic image during nitroglycerin test; **C and F,** superimposed endocardial and epicardial outlines before and during the brief nitroglycerin administration. The **arrows** separate the portion of the cardiac muscle that was potentiated by nitroglycerin from the characteristically thinned ischemic wall that failed to respond to nitroglycerin. Note that segment 1 did not respond to nitroglycerin as early as 30 minutes after LAD occlusion, as well as 5 hours after LAD occlusion. This segment proved to have >80% myocardial necrosis after the 5 hours of LAD occlusion (see also Figure 6). Segments 2 and 8 were potentiated by nitroglycerin 30 minutes after occlusion but not during subsequent nitroglycerin tests performed throughout the 5 hours of LAD occlusion. These segments exhibited 60 to 80% eventual necrosis. Segment 3 was potentiated both 30 minutes and 5 hours after LAD occlusion, and this segment proved to have myocardial necrosis <40%. Abbreviations as in Figure 4.

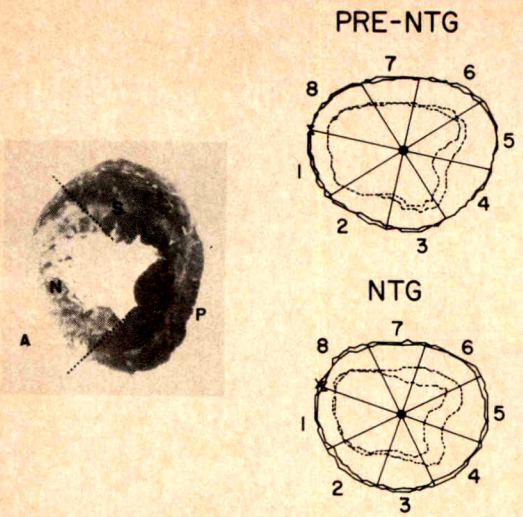

FIGURE 6. Triphenyl-tetrazolium-chloride stained left ventricular slab equivalent to low papillary 2-D echocardiographic cross section (from the same dog as in Figures 4 and 5), along with superimposed 2-D echocardiographic endocardial and epicardial outlines obtained before and during nitroglycerin (NTG) testing 5 hours after left anterior descending artery occlusion. Note that the size of the nitroglycerin nonresponsive region correlates well with the area of myocardial necrosis. A = anterior; N = myocardial necrosis area; P = posterior; S = interventicular septum.

extent of necrosis was 40 to 60%, nitroglycerin still caused significant potentiation in systolic fractional area change, but potentiation in systolic wall thickening was not significant. In those segments where the ultimate necrosis was found to be >60%, there was no potentiation with nitroglycerin in segmental LV function. In these segments further deterioration of segmental LV function was seen during nitroglycerin testing, but the decrease in function was not statistically significant.

The time course of the LV functional response to nitroglycerin in segments that exhibited ultimate necrosis >60%, is shown in Figure 3, both before and throughout the period of LAD occlusion. In segments where the ultimate extent of necrosis was 60 to 80%, significant nitroglycerin-induced augmentation in segmental LV function occurred before and at 30 minutes after LAD occlusion, but not at subsequent nitroglycerin test intervals during the 5-hour LAD occlusion (Figure 3, left). Thus, nitroglycerin failed to augment segmental LV function in these segments 1 hour after LAD occlusion. In segments where the ultimate necrosis was >80%, potentiation of segmental LV function in response to the nitroglycerin test was present before coronary artery occlusion, but there was no significant response of segmental LV function during the nitroglycerin test even as early as 30 minutes after the LAD occlusion (Figure 3, right).

Figures 4 and 5 show 2-D echocardiographic stop-frame images in end-diastole and end-systole, both before and during the nitroglycerin test, obtained before and 30 minutes as well as 5 hours after the LAD occlusion. Figure 6 shows a triphenyltetrazolium chloride–stained LV slab and compares it with the equivalent 2-D echocardiographically derived cross section studied 5 hours after LAD occlusion. These typical echocardiograms along with the superimposed computer-aided display illustrate the nitroglycerin potentiation in LV function before LAD occlusion and the absence of potentiation in segments that developed >60% necrosis 5 hours after LAD occlusion.

Discussion

It is clearly desirable and important to develop methods capable of differentiating potentially viable from irreversibly injured ischemic myocardium. Successful and accurate differentiation, preferably by reliable noninvasive diagnostic methods, may help anticipate and evaluate effects of appropriate treatments, such as bypass surgery or pharmacologic interventions.

In the current study, 2-D echocardiographic segmental analysis of LV short-axis cross sections after coronary occlusion revealed that remote nonischemic segments invariably exhibited significant nitroglycerin-induced functional augmentation. In the underperfused jeopardized zone, ischemic segments in which ultimate necrosis was <40% always exhibited significant nitroglycerin potentiation as late as 5 hours after occlusion. However, in segments in which necrosis was >60%, there was no potentiation of segmental LV function 5 hours after occlusion. We noted that significant nitroglycerin augmentation of segmental LV function was lost as early as 1 hour after LAD occlusion in segments with eventual 60 to 80% necrosis. In segments in which necrosis was >80%, there was no nitroglycerin potentiation even 30 minutes after occlusion.

Previous studies of nitroglycerin assessment of functional reserve: Nitroglycerin may improve cardiac contraction by reducing ventricular loading and altering the myocardial oxygen supply-to-demand ratio[11–16] and may also redistribute blood flow to ischemic zones.[1–10] Inotropic effects of nitroglycerin remain controversial.[1,6,12]

Previous clinical studies indicated that hypokinetic ventricular segments respond to nitroglycerin with improved wall motion, whereas areas of dyskinesia show almost no response.[11,13–15] Helfant et al[15] reported that a positive regional ventricular response to nitroglycerin appears to be predictive of corresponding regional benefits from coronary bypass surgery.[26] Banka et al[12] and Theroux et al[27] noted in experimental studies of acute coronary occlusion that nitroglycerin improved contraction of nonischemic and border zones, with reduction of potentiation toward the center of the ischemic zone. Bodenheimer et al,[19] in a clinical study, demonstrated that nitroglycerin-responsive LV areas were characterized by presence of histologically normal myocardium, whereas unresponsive areas were comprised of a significant amount of fibrosis or necrosis. These data suggested that reversal of asynergy in response to nitroglycerin signifies reversibly ischemic or normal myocardium. On the other hand, Komer et al[28] found no improvement in ischemic wall thickening abnormalities in any portion of the ischemic zones. The myocardial responsiveness of the border zone to nitroglycerin is still in dispute.

Myocardium with partial or patchy necrosis would be expected to have a complex functional response to nitroglycerin, because of interregional tethering[29] and vascular communication. Moreover, nitroglycerin has both beneficial and deleterious effects on ischemic myocardium, depending primarily on the resulting increase in heart rate and reduction in systemic pressure.[3,17,27,30]

The present study related regional myocardial necrosis to myocardial function. We found that nitroglycerin could improve wall motion abnormalities in ischemic zones, and that the region which did not respond to nitroglycerin correlated well with the extent of measured myocardial necrosis (Fig. 6).[22,31]

Limitations of our study: There are evident limitations in this study. Thus, although we carefully matched 2-D echocardiographic cross sections with equivalent excised LV slabs, using every available cardiac muscle landmark for structural reference, the 2 sections may not be quite the same. It is also necessary to recognize that pathologic slabs may change their size and become somewhat distorted. The relatively small number of segments studied and high variability in systolic wall thickening measurements (Table II) may limit definite statistical evaluation. Thus, the discrepancy between systolic fractional area change and systolic wall thickening noted in the group of 41 to 60% necrosis (Fig. 2) may be due to a small sample number. Our present study could not ascertain the ultimate fate of nitroglycerin-potentiated segments, nor could it exclude potential viability of segments that failed to be potentiated early after coronary occlusion, but might have been treated at that time by reperfusion.

Clinical applications: This study indicates that 2-D echocardiography of LV segments during brief periods of nitroglycerin infusion can help characterize the functional reserve of myocardium during acute ischemia in dogs. The experimental data may not be simply applicable to the human subject. Thus, myocardial response to nitroglycerin in patients with chronic coronary artery disease could be affected by collateral circulation, old fibrosis, and the number of vessels involved. Nevertheless, our experimental data suggest that myocardial areas that improve function by nitroglycerin testing may be judged to be sufficiently viable to allow rational therapy. Thus, 2-D echocardiographic nitroglycerin testing during treatment of patients with acute myocardial infarction may prove useful for assessment of interventions and their effectiveness.

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Nuclear Magnetic Resonance Imaging of Acute Myocardial Infarction in Dogs: Alterations in Magnetic Relaxation Times

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Nuclear magnetic resonance (NMR) imaging was used to study 24-hour-old acute myocardial infarctions in 8 dogs. Images and measurements of excised hearts were obtained in a 6.5 ml bore-resistive NMR imager (0.35 Tesla). Spin echo NMR imaging in each instance demonstrated the area of infarction as a region of increased signal intensity compared with that in normal myocardium. The T1 and T2 values of the area of infarction were greater than those of normal myocardium in all dogs. For each dog the T1 value was greater for the infarct region; however, the group mean value for T1 (ms) of the infarct region (728 ± 94) was not significantly greater than that for the normal region (650 ± 87). The T2 value (ms) was discriminate for all dogs, and the mean value for the infarct region (48 ± 2) was significantly different ($p < 0.01$) from the value for normal myocardium (42 ± 1). The percent water content of the infarct (79 ± 1%) was significantly greater ($p < 0.01$) than that of normal regions (76 ± 1%). The linear relationship between T2 value and percent water content showed a good correlation coefficient ($r = 0.90$; $p < 0.01$).

NMR imaging detects acute myocardial infarction as a positive image without contrast media. Increased signal intensity of the infarct is related to increased hydrogen density and increased T2 relaxation time.

Coronary heart disease is the major cause of morbidity and mortality in industrialized countries. Nuclear magnetic resonance (NMR) imaging has some intrinsic advantages for the study of the cardiovascular system and myocardial disease. Because flowing blood generates little or no NMR signal, there is high natural contrast between the lumen and walls of blood vessels and cardiac chambers,[1,2] which is attained without the use of contrast medium. In addition, tissue characterization can be attained from analysis of magnetic relaxation times (T1 and T2) of tissues.[3,4]

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Magnetic relaxation times of tissues have been found to be altered by pathologic processes,[3,4] particularly processes that increase the water content of tissues.[5,6] Myocardial ischemic damage is associated with predictable increases in regional myocardial water content.[6,7] In a recent study the relaxation times of normal and infarcted myocardial samples were measured using an inversion recovery technique, and a significant increase was found in T1 relaxation times of infarcted myocardium.[6] However, the only previously reported study that attempted to image ex situ infarcted hearts with NMR failed to discriminate infarcted from normal myocardium unless contrast media were administered.[8] The area of nonperfusion was only demonstrated by using a paramagnetic contrast medium (manganese).

This study was undertaken to determine whether NMR imaging techniques more sensitive to myocardial edema would result in the detection of acute myocardial infarction (MI) without contrast media and to define the alterations in magnetic relaxation times associated with myocardial ischemia injury. The relation between changes in myocardial relaxation times and myocardial water content also were assessed.

TABLE I Individual Values for T1, T2, and Percent Water Content

	Infarcted Myocardium			Normal Myocardium		
Dog	T1 (ms)	T2 (ms)	Water (%)	T1 (ms)	T2 (ms)	Water (%)
1	694	45.4	78.4	620	42.8	76.7
2	640	45.7	77.5	549	40.8	76.3
3	599	48.8	78.5	538	43.0	75.2
4	803	52.0	79.2	710	40.2	75.9
5	876	49.2	78.2	771	42.3	75.9
6	758	50.5	78.6	713	43.5	77.3
Mean	728.3	48.4	78.6	650.2	42.1	76.2
SD	94.8	2.4	0.7	87.4	1.2	0.6

SD = standard deviation.

Methods

Eight adult mongrel dogs (weighing 15 to 21 kg) were used in this study. Six dogs underwent operative ligation of the left anterior descending coronary artery (distal to the first septal branch) and 2 dogs served as sham animals. Twenty-four hours after coronary arterial ligation the dogs were killed by administering pentobarbital. NMR imaging was performed 60 to 90 minutes after cardiectomy.

The excised hearts were placed within the 6.5 cm aperture of the small animal NMR imager. This is a resistive NMR imager with a field strength of 0.35 Tesla (15 MHz hydrogen resonant frequency). Five simultaneous cross-sectional levels (5 mm in thickness) were imaged in 6.5 minutes. Spatial resolution was 1.5 mm × 1.5 mm × 4 mm. The hearts were imaged from apex to the base of the heart using 2 contiguous image volumes each consisting of 5 contiguous 5-mm transverse (axial) images.

The NMR imaging technique was the spin echo sequence described in detail previously.[9] At each cross-sectional level 4 different images were obtained by using a combination of 2 pulse sequence intervals (500 and 1,000 ms) and 2 echo delay times (28 and 56 ms).

Because the area of MI was most clearly discernible on images obtained with a 1,000-ms pulse interval and 56-ms echo-delay time (1,000/56), the regions of interest for T1 and T2 relaxation times were outlined on the 1,000/56 image. The T1 and T2 relaxation times were determined by a method described previously.[3] For each heart the T1 and T2 relaxation times were average values determined from 6 separately defined regions of interest. The regions of interest were manually drawn over the anterior wall of the left ventricle (infarct) or over the posterior wall (normal myocardium). The regions of interest over the anterior and posterior walls were equivalent in area. For the sham animals regions of interest were determined over the same 2 areas.

After completion of the imaging procedure the hearts were sliced transversely (from apex to base) at 10 mm intervals. The perimeter of each myocardial slice and the area of gross MI was traced on clear film overlays for subsequent comparison with NMR images. The area of gross MI was clearly visible on each myocardial slice. Incubation of the myocardial slice in a histochemical stain was not used to further define the MI in this study because of the desire to measure true wet and dry weights of myocardial samples. Moreover, 24-hour-old infarcts are clearly defined without histochemical staining. For each heart, 5 myocardial samples were cut from the center of the infarct and 5 from the normal posterior wall of the myocardial slices. With the sham hearts 5 samples were obtained from both the anterior and posterior walls of the myocardial slices. After blotting dry these samples were weighed (wet weight) on an Ainsworth balance. The samples were weighed again after dessication to a constant dry weight in a dessicating oven (HEET-CAB, Lab-Line Instruments) for 48 to 72 hours. The percent water content was calculated as [(wet weight − dry weight)/wet weight] × 100%. The percent water content reported for the infarct or the normal myocardium of each heart represents the mean value of 5 individual tissue samples.

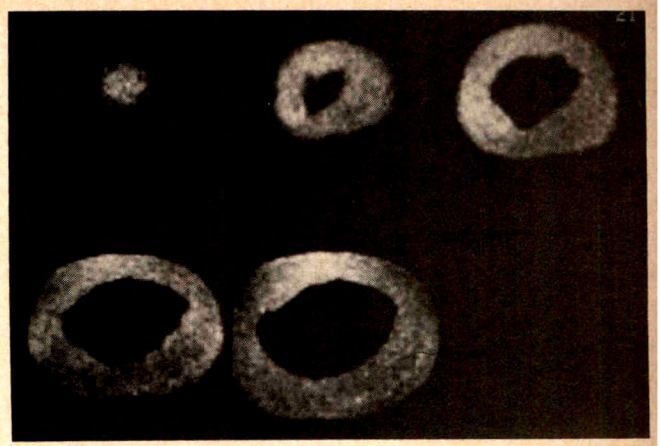

FIGURE 1. Sequential cross-section nuclear magnetic resonance images extending from the apex to mid-portion of the left ventricle in a dog at 24 hours after ligation of the left anterior descending coronary artery. The high intensity area (**increased brightness**) involves almost the entire cross-sectional area (**left upper slices**) in the 2 caudal sections. On the most cranial slice the high intensity region is confined to the anterior wall. Images are viewed from above.

Data analysis and statistics: For each infarcted heart and sham heart the percent differences in magnetic relaxation times (T1 or T2) between infarcted and normal myocardium were calculated. In this manner each animal served as its own control for defining changes in relaxation times with the ischemic intervention. The following formula was used for these calculations: Percent difference T1 (or T2) = ([T1 (or T2) infarct − T1 (or T2) normal]/[T1 (or T2) normal]) × 100%.

The group data for T1, T2, and percent water content for the infarcted and normal regions of infarcted hearts are reported as mean values ± standard deviation. The data for sham animals are presented as a mean value and range because only 4 values (anterior and posterior wall from 2 animals) were obtained. Again, the T1 and T2 values (for each individual animal) represents the mean of values calculated

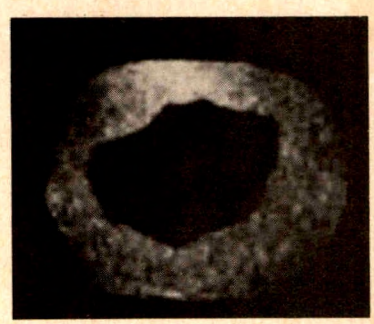

FIGURE 2. Cross-sectional NMR image through the mid-portion of the left ventricle shows a high intensity area in the anterior wall of the left ventricle. Image is viewed from above.

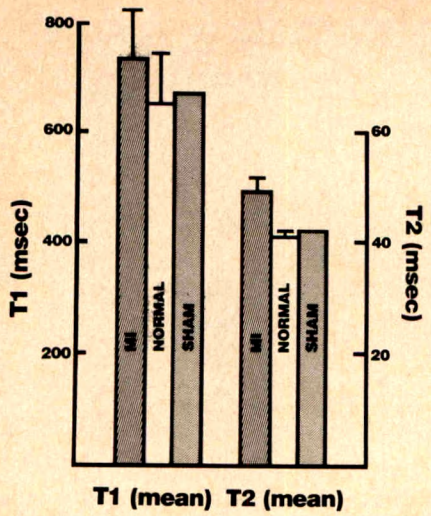

FIGURE 3. Block diagram showing the mean values ± standard deviation for T1 and T2 values for infarcted myocardium (MI) and normal myocardium (NORMAL) of dogs with 24-hour-old myocardial infarctions. The value for sham animals is also shown.

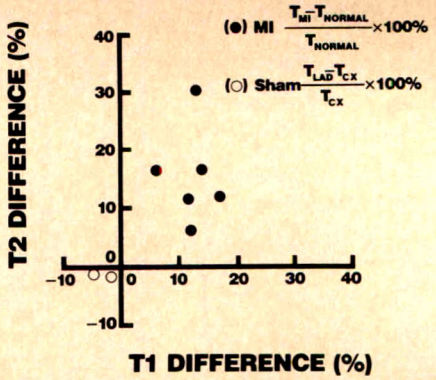

FIGURE 4. Percent differences in T1 and T2 values between normal and infarcted myocardium plotted for each of the 6 dogs with infarcts. Similarly, the percent differences for relaxation times of the left anterior descending coronary artery (LAD) and circumflex (CX) distribution are plotted for the 2 sham dogs.

from 6 separately defined regions of interest within the infarcted or normal myocardium (as previously described).

Differences in the mean values for T1, T2, and percent water content between infarcted and normal myocardium were compared for statistical significance using the paired *t* test. The relation between T1 or T2 and percent water content was analyzed with the least-squares fit for linear regression.

Results

Pathologic findings: Gross MI involved the anterior wall of each transverse myocardial slice caudal to the ligature at postmortem examination in all 6 dogs. The infarct extended from the ligature on the proximal left anterior descending coronary artery to the apex of the left ventricle. Almost the entire circumference of the most caudal (apical) slice consisted of infarcted tissue. In some animals the infarct also extended into the lateral wall or the anterior portion of the septal wall. The entire posterior wall and the posterior half of the septal wall were free of infarction in all animals. In the 2 sham animals, MI was absent.

The mean percent water content of infarcted myocardium (79 ± 0.7%) was significantly greater ($p < 0.01$) than that of the normal myocardium (76 ± 0.6%) (Table I). The mean percent water content of the myocardium of sham animals was 76% (range 76 to 77%). The percent water content in the area of distribution of the left anterior descending artery was nearly identical to that in the myocardium supplied by the circumflex coronary artery in the 2 sham animals.

NMR image of acute myocardial infarction: The NMR intensity of the area of MI was perceptively increased on NMR images in all 6 dogs. In conformity with gross pathologic findings, the region of increased intensity always involved the anterior segment (Fig. 1 and 2) and most of the circumference of the 2 caudal (apical) slices (Fig. 1). There was no area of increased signal intensity in the 2 sham animals.

T1 and T2 relaxation times: When considering the animals as a group, the mean value for T1 relaxation times of infarcted myocardium (728 ± 95 ms) was not significantly greater than the value for normal myocardium (650 ± 87 ms) (Fig. 3). There was a wide range of T1 values for infarcted and normal myocardium, and overlap of individual T1 values between infarcted and normal myocardium (Table I). The T1 value of the infarcted myocardium was greater than that of normal myocardium for each individual animal. The percent differences in T1 values of infarcted compared with normal myocardium, when each dog was used as its own control, are depicted in Figure 4.

The mean value for T2 relaxation time of infarcted myocardium (48 ± 2 ms) was significantly greater ($p < 0.01$) than that of normal myocardium (42 ± 1 ms) (Fig. 3). There was a narrow range of T2 values for normal myocardium (40 to 43 ms) and no overlap of individual values between the infarcted and normal groups (Table I). The percent differences in T2 values of infarcted compared with normal myocardium when each dog was used as its own control are depicted in Figure 4.

No significant relation was noted between T1 relaxation and the water content of myocardium ($r = 0.47$; difference not significant) (Fig. 5). A good correlation ($r = 0.90$, $p < 0.01$) was seen in the linear relation between T2 values and percent water content of myocardial samples (Fig. 6).

Discussion

Regions of acute MI showed increased signal intensity on NMR images with use of the spin echo technique. With the spin echo technique, signal intensity is determined by hydrogen density as well as by the T1 relaxation time and T2 relaxation times of the tissue. Intensity increases with greater hydrogen density, shortening of T1, and lengthening of T2 relaxation time. The spin echo technique tends to accentuate T2 differences between tissues compared with some other techniques, like inversion recovery, which emphasize

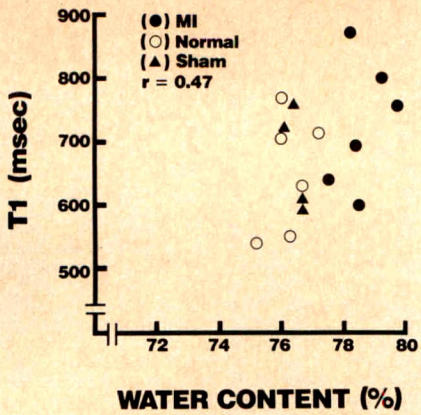

FIGURE 5. T1 relaxation times plotted against the percent water content. Values are given for infarcted and normal myocardium (MI) of infarcted dogs and for the left anterior descending artery and circumflex areas of the 2 sham animals.

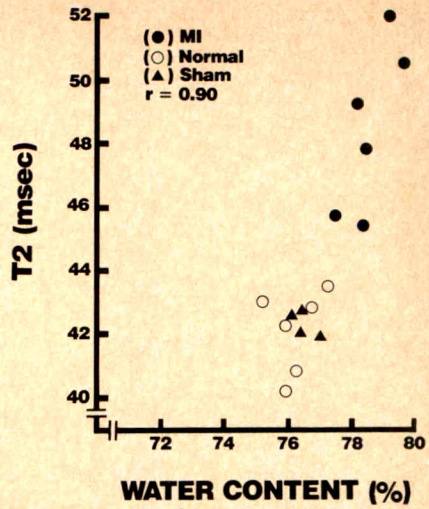

FIGURE 6. T2 relaxation times plotted against the percent water content. Format is the same as for Figure 5.

T1 differences. The current study indicated that both the T1 and T2 values of infarcted myocardium were increased compared with values of normal myocardium. The increase of T1 value would tend to decrease the signal intensity of NMR images. Consequently, the increase in intensity observed in the area of infarcted myocardium indicates preponderance of the influence of a prolonged T2 relaxation time and increased hydrogen density in the formation of the spin echo images.

Two earlier reports demonstrated increases in T1 relaxation time of ischemically injured myocardium that parallel increases in myocardial water content. The current study did not find a close relation between T1 and myocardial water content.[6,10] Previous studies[3,11] and the current one also found increased T2 relaxation time in abnormal tissues, particularly edematous tissues.

The finding of a significant increase in T2 values of ischemically damaged myocardium is unique to this study, as is the observation that the area of myocardial damage shows an increase in NMR signal intensity. Previous reports have indicated either that the ischemically damaged myocardial region is represented by a poorly defined area of diminished signal intensity on NMR images[12] or that the ischemically damaged area can only be recognized as a perfusion defect after intravenous administration of a paramagnetic substance (manganese).[8] The diametric conclusions of the current report and previous ones[8,9] may be a consequence of a difference in NMR imaging techniques because the spin echo technique tends to accentuate T2 differences as well as hydrogen density of tissues.[13] The importance of the NMR imaging characteristics of ischemically damaged myocardium with use of the spin echo technique (as applied in the current study) is that the pathology is represented as a positive image (increased intensity) and infarcted myocardium is discriminated from normal myocardium without the need for contrast media.

The T2 relaxation times of normal and infarcted myocardium also were linearly related to local water content. In fact, there was a greater correlation for T2 values and water content than there was for T1 value and water content as found in previous studies.[6,10] Moreover, there was a sharp boundary between the ranges of T2 values of infarcted and normal myocardium. This contrasted with the overlap of individual T1 values of normal and infarcted myocardium among the group of animals.

The findings in this study are consistent with data obtained in a rat model of muscle infarction.[11] The muscle of the infarcted hind leg showed significant prolongation of T1 and T2 relaxation times compared with the normal contralateral leg. The T2 relaxation rates displayed closer relationship to the percent water content of the muscles than the T1 relaxation rates.

The current study as well as a number of previous studies reveal the advances in diagnosis offered by NMR imaging; normal tissues and pathologic processes may be characterized by their relative T1 and T2 relaxation processes.[3–6,10,11] Optimistic conjecture would envision early assessment of the effects of therapeutic intervention by defining T1 and T2 values using NMR imaging of ischemic processes. With proton NMR imaging, tissue characterization must be shown to have clinical efficacy because the anatomic information provided by NMR imaging is similar to that achieved by computed tomography and ultrasonography. A distinct advantage of NMR imaging in ischemic heart disease and other cardiovascular diseases is the ability to define internal cardiac topography without the need for contrast media. This is particularly important in acute myocardial ischemia and infarction because currently used contrast media have potentially deleterious hemodynamic and electrophysiologic effects.[14]

The application of NMR imaging to heart disease is complicated by cardiac and respiratory motion. Motion degrades NMR images by decreasing signal intensity rather than by introducing artifacts as occurs with computed tomography. The recent demonstration of excellent NMR images of the heart with use of cardiac

gating by 2 groups[15,16] indicates the early feasibility of clinical NMR imaging for the evaluation of heart disease. A technique for rapid acquisition of NMR images within a 40- to 50-ms period may also be useful for NMR imaging of the heart.[17]

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Effects of Coronary Occlusion on Flow in the Distribution of a Neighboring Stenotic Coronary Artery in the Dog

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The effect of left anterior descending coronary artery (LAD) occlusion on flow through a severely stenotic left circumflex artery (LC) was studied in 19 open-chest dogs. In 8 dogs (Group 1) aortic pressure, distal circumflex pressure, circumflex flow, and heart rate were measured. In the absence of an LC stenosis, LAD occlusion resulted in an increase in LC flow from 32 ± 3 to 41 ± 5 ml/min ($p < 0.001$). In the presence of a severe LC stenosis produced with a snare, LAD occlusion resulted in a decrease in distal LC pressure (54 ± 2 to 30 ± 1 mm Hg; $p < 0.001$), an increase in resistance across the LC stenosis (1.8 ± 0.2 to 3.5 ± 0.4 units; $p < 0.001$) and a decrease in flow through the LC (24 ± 2 to 20 ± 2 ml/min; $p < 0.001$). Aortic pressure did not change significantly (94 ± 3 to 93 ± 3 mm Hg) and heart rate increased slightly (90 ± 5 to 104 ± 5 beats/min; $p < 0.001$). LAD occlusion, therefore, increased the severity of the LC stenosis and resulted in a decrease in LC flow. The decrease in intraluminal pressure distal to the LC stenosis, and thus in the stenotic segment itself, may have resulted in passive narrowing of the stenotic segment, which may have been responsible for the decrease in flow.

In 11 dogs (Group 2) the LC stenoses were produced so that anterograde flow through the stenotic LC artery did not change significantly after LAD occlusion. However, LAD occlusion resulted in a decrease in flow (measured with radioactive microspheres) to the area supplied by the stenotic LC artery (0.62 ± 0.02 to 0.50 ± 0.09 ml/min/g; $p < 0.05$), possibly because collateral flow from the LAD to the LC-dependent myocardium was interrupted. In addition, LAD occlusion resulted in selective underperfusion of the subendocardial layers of the LC-dependent area (endocardial/epicardial flow ratio from 0.89 ± 0.07 to 0.40 ± 0.10; $p < 0.005$), possibly because of a combination of a decrease in perfusion pressure distal to the stenoses (54 ± 4 to 39 ± 3 mm Hg; $p < 0.005$) and an increase in left ventricular end-diastolic pressure (from 6 ± 1 to 13 ± 2 mm Hg; $p < 0.005$).

The results of these studies demonstrate mechanisms by which myocardial ischemia may occur in the area supplied by a stenotic coronary artery if a neighboring coronary artery becomes occluded.

Many patients with acute myocardial infarction have significant stenoses in coronary arteries other than the one supplying the infarcted area.[1] In 1940, Blumgart et al[2] discussed the concept of "infarction at a distance." In this situation, myocardium in the distribution of an occluded coronary artery is dependent on collaterals from a second coronary artery. If the second artery becomes acutely occluded, infarction may occur in the collateral-dependent area which is "distant" from the area of acute occlusion.

Recently Schuster and Bulkley[3,4] reported that some patients with acute myocardial infarction had postinfarction ischemia in an area of myocardium distant from the infarcted area. These patients had atherosclerotic narrowing with superimposed thrombotic occlusion of the artery supplying the infarcted area and a severe stenosis of the artery supplying the remote ischemic area. These studies suggest that occlusion of a coronary artery may have a deleterious effect on myocardium supplied by a neighboring stenotic artery.

It has previously been shown in animal models that interventions that dilate the distal bed of a coronary artery with a severe, nonfixed stenosis result in a decrease in pressure distal to the stenosis, an increase in stenosis resistance, and a decrease in flow through the stenotic artery.[5,6] The dilation-induced decrease in pressure distal to the stenosis, and thus in the stenotic segment itself, may cause partial collapse of the stenotic segment, resulting in the observed increase in stenosis resistance and reduction in flow.[5,6] Other interventions that dilate the distal arteriolar bed of a stenotic coronary artery might also cause a decrease in distal coronary pressure and a passive increase in stenosis resistance. Occlusion of a neighboring coronary artery could interrupt collateral flow to the myocardium supplied by

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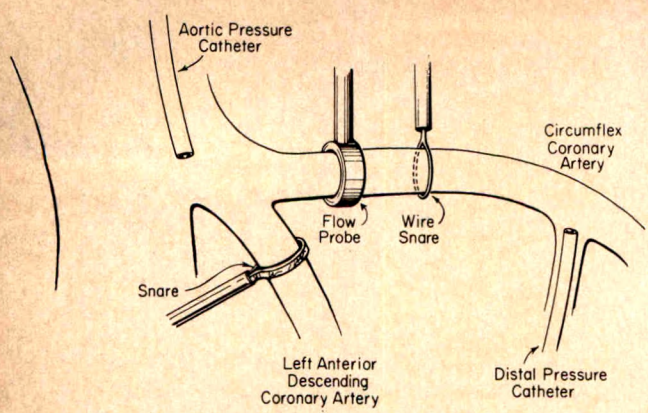

FIGURE 1. Experimental preparation.

a stenotic artery, increase the contractile force of the myocardium supplied by the stenotic artery, and increase the heart rate. All of these changes could cause dilation of the distal bed of the stenotic artery, a reduction in pressure distal to the stenosis, passive collapse of the stenotic segment, and a decrease in flow through the stenotic artery. The decrease in flow through the stenotic artery could result in ischemia distant from the myocardium supplied by the occluded artery.

Occlusion of a coronary artery could also cause a decrease in total flow to myocardium supplied by a neighboring stenotic artery simply by interrupting collateral flow to the area. Furthermore, subendocardial perfusion could be impaired by the combination of a decrease in pressure distal to the stenosis caused by distal bed dilation and an increase in left ventricular diastolic pressure.[7–9] Both a decrease in collateral flow and a selective decrease in subendocardial flow could result in ischemia in an area of myocardium supplied by a stenotic artery distant from an area of complete coronary occlusion.

This study, therefore, was performed to evaluate these potential mechanisms of ischemia in the distribution of a stenotic coronary artery when a neighboring coronary artery is occluded.

Methods

The studies were performed in 19 open-chest dogs anesthetized with intravenous alpha chloralose (100 mg/kg) and intramuscular morphine (2 mg/kg). The mean weight of the dogs was 24 ± 1 kg (range 21 to 32 kg). Respiration was controlled with a Harvard respirator pump through a cuffed endotracheal tube. A left thoracotomy was performed. The proximal portion of the left circumflex coronary artery (LC) was dissected free and was instrumented as shown in Figure 1. A PE 50 catheter was inserted into a branch of the LC for measurement of distal coronary arterial pressure. A PE 200 catheter was advanced through the femoral artery into the ascending aorta for measurement of aortic pressure. Statham P23ID pressure transducers were used. Before each experiment, each transducer system was calibrated with a mercury manometer.

The stenosis was produced with an external wire snare placed around the LC proximal to the coronary pressure catheter. The snare consisted of soft wire attached through polyethylene tubing to a machinist's micrometer so that precise adjustments of the degree of arterial narrowing could be made. A 2.0 or 2.5 mm flow probe was placed around the LC proximal to the snare. A Statham P2202 electromagnetic flowmeter was used. Distal LC pressure was monitored while the flow probe was put in place. The size of the probe was chosen so that it gave a good quality flow signal without changing LC pressure distal to the probe. Zero flow, obtained by transient complete occlusion of the LC, was checked frequently during the course of each experiment.

A portion of the mid left anterior descending artery (LAD) was also dissected free. A snare consisting of umbilical tape passed through polyethylene tubing was placed around the artery. Complete occlusion of the LAD was accomplished by tightening this snare.

All animals received an infusion of 1 mg/min of lidocaine throughout the procedure. Extra boluses of lidocaine were administered as necessary to control ventricular arrhythmias.

The dogs were classified into 2 groups. In Group 1, consisting of 8 dogs, the effect of occlusion of the LAD on anterograde flow through the stenotic LC was studied. Aortic pressure, distal LC pressure, LC blood flow, and lead II of the electrocardiogram were recorded before and after complete occlusion of the LAD. The LAD was first temporarily occluded in the presence of a normal LC. The LC was then progressively narrowed by tightening the wire snare, after which the LAD was again occluded. This procedure was repeated until the LC stenosis was severe enough so that occlusion of the LAD resulted in a decrease in flow through the LC.

In Group 2, consisting of 11 dogs, regional myocardial blood flow was measured with radioactive microspheres. The experimental preparation was identical to that previously described except for the addition of a left atrial catheter through which the microspheres were injected and a fluid-filled catheter inserted through the apex of the left ventricle for left ventricular pressure measurement. In each dog regional myocardial blood flow was measured before and after complete occlusion of the LAD in the presence of a normal LC and again in the presence of a severely stenotic LC. So that the order of the experiments did not affect our results, normal LC arteries were studied first in some dogs and stenotic arteries were studied first in others. The LC stenoses were produced by tightening the wire snare. The purpose of this portion of the study was to evaluate the effect of LAD occlusion on transmural flow in the distribution of a stenotic LC artery when anterograde flow through the stenotic LC did not change. In the total group of dogs there was no significant change in flow through the stenotic LC after LAD occlusion.

In the entire group of dogs, the LC stenosis was stable for a mean of 10 ± 2 minutes before LAD occlusion. The LAD was occluded for a mean of 4 ± 0.4 minutes. Hemodynamic measurements were recorded a mean of 83 ± 7 seconds after the onset of LAD occlusion.

Fifteen μm diameter microspheres (3M Company) were used to measure regional myocardial blood flow. They were diluted in 10% low molecular weight dextran and approximately 5×10^6 microspheres were injected. Before injection the microspheres were mixed in a vortex agitator and an ultrasonic bath for at least 15 minutes. In each study, microspheres were used which were labeled with 4 of the following isotopes: iodine-125, cerium-141, cobalt-57, niobium-95, scandium-46, strontium-85, tin-113, or chromium-51. The microsphere suspension was injected into the left atrium over a 15-second period and the atrial line was flushed with 10 ml of isotonic saline solution. Beginning simultaneously with the microsphere injection and continuing for 90 seconds, a ref-

TABLE I Effect of Left Anterior Descending Artery (LAD) Occlusion on Left Circumflex Artery (LC) Pressures and Flow in the Absence of LC Stenosis and in the Presence of Severe LC Stenosis (Group I)

	Mean Aortic Pressure (mm Hg)	Mean Distal Circumflex Pressure (mm Hg)	Mean Stenosis Pressure Gradient (mm Hg)	Mean Distal Circumflex Resistance (mm Hg/ml/min)	Mean Stenosis Resistance (mm Hg/ml/min)	Mean Circumflex Blood Flow (ml/min)	Heart Rate (beats/min)
				No Left Circumflex Artery Stenosis			
Control	95 ± 4	84 ± 4	. . .	3.1 ± 0.4	. . .	32 ± 3	106 ± 6
LAD occlusion	90 ± 5	79 ± 5	. . .	2.2 ± 0.3	. . .	41 ± 5	122 ± 6
	p <0.01	p <0.01	. . .	p <0.001	. . .	p <0.001	p <0.005
				Severe Left Circumflex Artery Stenosis			
Control	94 ± 3	54 ± 2	40 ± 2	2.4 ± 0.2	1.8 ± 0.2	24 ± 2	90 ± 5
LAD occlusion	93 ± 3	30 ± 1	63 ± 2	1.6 ± 0.1	3.5 ± 0.4	20 ± 2	104 ± 5
	NS	p <0.001	p <0.001	p <0.001	p <0.001	p <0.001	p <0.001

NS = not significant.

erence sample of arterial blood was drawn from the aortic catheter at a constant rate of 15 ml/min.

At the end of the experiment 10 ml of Evans blue dye was injected into the LC at systemic pressure. The animals were then killed and the hearts were removed, weighed, and fixed in 10% buffered formalin. The posterior papillary muscle region was supplied by the LC in each dog as documented by its blue staining. This region was therefore taken to represent the myocardium under study. This region was divided into 4 transmural layers of equal thickness, with layer 1 being the layer closest to the epicardium and layer 4 being the layer closest to the endocardium. The papillary muscle was called layer 5. Similar myocardial specimens were taken from the anterior wall in the distribution of the LAD and were divided into 4 transmural layers of equal thickness, with layer 1 being closest to the epicardium and layer 4 being closest to the endocardium. All myocardial sections were weighed and placed in vials for counting.

All sections were counted in a Packard model 5912 gamma spectrometer with a multichannel analyzer at window settings selected to correspond to the peak energies of each radionuclide. The activities recorded in each energy window were corrected for background activity and for overlapping counts contributed by the accompanying isotopes with a digital computer. Blood flow was calculated by using the reference arterial blood sample during the injection of microspheres. Knowing the rate of withdrawal of the reference sample (Qr) and the radioactivity in the reference sample (Cr), and assuming that the ratio of flow and radioactivity is identical in all organs because uniform mixing of microspheres with blood occurs during passage through the left ventricle, myocardial blood flow (Qm) was determined by measuring the myocardial radioactivity (Cm) and calculating $Qm = Qr \cdot Cm/Cr$. Myocardial blood flow (ml/min) was divided by the corresponding sample weight and was expressed as ml/min/g of myocardium.

Hemodynamic measurements were recorded on a Hewlett-Packard 7758B recorder at paper speeds of 1 to 25 mm/s. Mean resistance across the stenotic segment was calculated using the formula $R = (P1 - P2)/Q$ and was expressed in resistance units (mm Hg/ml/min), where P1 = mean aortic pressure, P2 = mean distal LC pressure, and Q = mean LC coronary blood flow. Distal LC resistance was calculated by dividing mean distal LC pressure by LC flow.

All data are shown as mean values ± the standard error of the mean. Significance of the differences for the hemodynamic data was determined by Student's *t* test for paired observations.[10] Significance of differences for the microsphere flow data was determined by 2-way analysis of variance.[10]

Results

In the dogs in Group I, the LAD was first occluded in the presence of a normal LC. The results are shown in Table I, and an example is shown in Figure 2. As seen in Table I, there was a small increase in heart rate and a small decrease in aortic and distal coronary pressure. Mean blood flow through the LC increased from 32 ± 3 to 41 ± 5 ml/min.

As a stenosis was applied to the LC and was made more severe, there was a smaller increase in blood flow through the LC in response to LAD occlusion. The effects of LAD occlusion on the hemodynamics of a severely stenotic LC are shown in Table I and Figure 3. As shown in Table I, there was a small increase in heart rate and aortic pressure did not change significantly. The distal coronary pressure decreased, however, and the pressure gradient across the stenosis increased. There was also a marked and significant increase in stenosis resistance, and flow through the stenotic artery actually decreased significantly.

In the 11 dogs in Group 2, regional myocardial blood flow was measured before and after LAD occlusion in the presence of a normal LC and in the presence of a stenotic LC. The stenoses were produced so that minimal changes in anterograde flow would occur through the stenotic LC in response to LAD occlusion. In each dog complete LAD occlusion was confirmed by the finding of a decrease in flow from 0.61 ± 0.05 to 0.05 ± 0.01 ml/min/g in the region of the anterior LV wall after LAD occlusion.

The hemodynamic effects of LAD occlusion in dogs in Group 2 in the absence of a LC stenosis are shown in Table II. The data are similar to those dogs without a stenosis in Group 1.

In the myocardial region supplied by the normal LC, regional flow measured with radioactive microspheres also increased after LAD occlusion (0.85 ± 0.04 to 1.05 ± 0.07 ml/min/g, $p < 0.05$). The change in flow in each

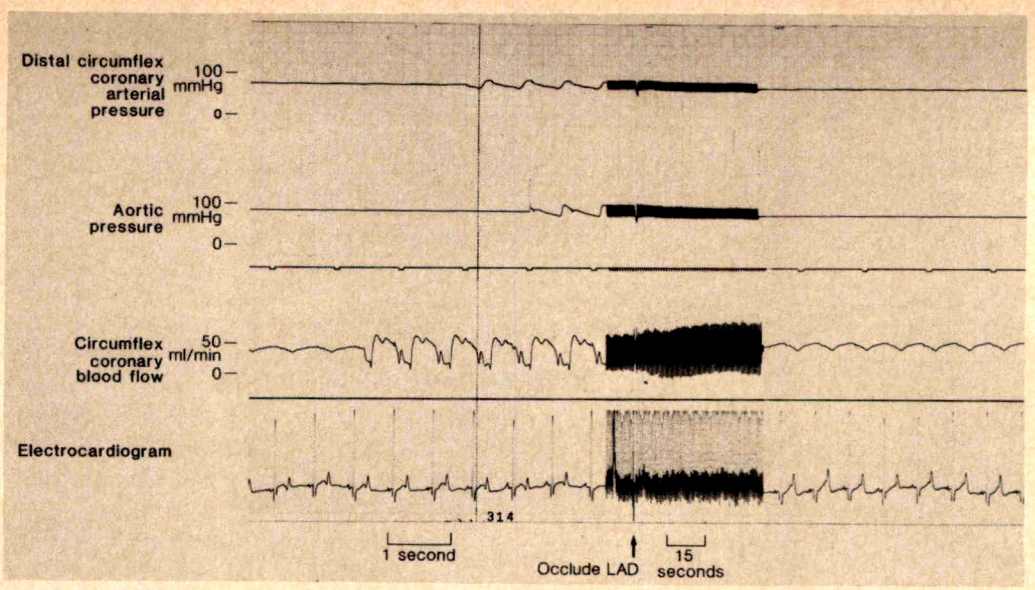

FIGURE 2. Effects of left anterior descending (LAD) coronary occlusion on pressure and flow in a normal circumflex artery. Mean pressures and flow are shown on the **left** and **right** and phasic pressures and flow in the **center.** Aortic and distal circumflex pressures decreased slightly and circumflex flow increased.

transmural layer is shown in Figure 4. In the absence of a LC stenosis, the endocardial/epicardial ratio did not change significantly in response to LAD occlusion (0.86 ± 0.10 to 0.81 ± 0.11).

The hemodynamic effects of occlusion of the LAD in dogs in Group 2 in the presence of an LC stenosis are shown in Table II. As can be seen, aortic pressure did not change significantly. Both mean and diastolic coronary pressure distal to the stenosis decreased significantly. Left ventricular end-diastolic pressure increased significantly, and there was a small but significant increase in heart rate. In individual dogs, LAD occlusion resulted in a small increase or decrease in total anterograde flow through the stenotic LC, but in the total group of dogs flow did not change significantly.

The changes in transmural flow measured with microspheres in the distribution of the stenotic LC in response to LAD occlusion are shown in Figure 5. Sub-

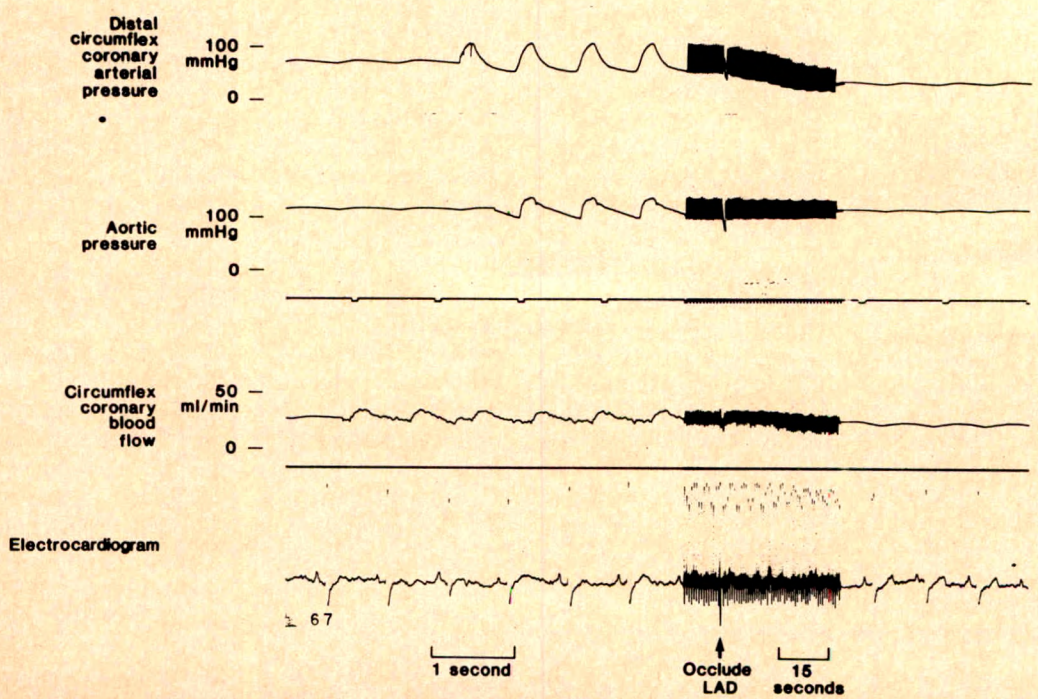

FIGURE 3. Effects of left anterior descending (LAD) coronary occlusion on pressure and flow in a severely stenotic circumflex artery. Mean pressures and flow are shown on the **left** and **right** and phasic pressures and flow in the **center.** Aortic pressure did not change, and distal circumflex pressure and circumflex flow decreased.

TABLE II Effect of Left Anterior Descending Artery (LAD) occlusion on Left Circumflex Artery (LC) Pressure and Flow in the Absence of Stenosis and in the Presence of LC Stenosis (Group 2)

	Mean Aortic Pressure (mm Hg)	Mean Distal Circumflex Pressure (mm Hg)	Diastolic Distal Circumflex Pressure (mm Hg)	Left Ventricular End-Diastolic Pressure (mm Hg)	Mean Circumflex Blood Flow (ml/min)	Stenosis Resistance (mm Hg/ml/min)	Heart Rate (beats/min)
				No Left Circumflex Artery Stenosis			
Control	102 ± 8	93 ± 7	85 ± 7	4 ± 2	46 ± 5	. . .	120 ± 7
LAD occlusion	100 ± 9	91 ± 8	83 ± 7	6 ± 1	61 ± 8	. . .	138 ± 8
	NS	NS	NS	p <0.025	p <0.001	. . .	p <0.025
				Left Circumflex Artery Stenosis			
Control	99 ± 6	54 ± 4	39 ± 4	6 ± 1	30 ± 3	1.6 ± 0.2	105 ± 6
LAD occlusion	94 ± 4	39 ± 3	25 ± 2	13 ± 2	28 ± 4	2.5 ± 0.5	130 ± 9
	NS	p <0.005	p <0.005	p <0.005	NS	NS	p <0.01

NS = not significant.

epicardial flow did not change significantly. However, flow in subendocardial layers 4 and 5 decreased significantly. Total transmural flow to the region supplied by the LC artery decreased slightly but significantly in response to LAD occlusion (0.62 ± 0.02 to 0.50 ± 0.09 ml/min/g; $p < 0.05$). The endocardial/epicardial ratio decreased from 0.89 ± 0.07 to 0.40 ± 0.10 ($p < 0.005$).

Discussion

In the absence of LC stenosis, occlusion of the LAD resulted in an increase in LC blood flow as measured with the electromagnetic flowmeter. An increase in flow in a coronary artery in response to occlusion of an adjacent coronary artery has been described previously.[11–14] There are several possible explanations for this finding. First, when pressure in the LAD decreases as a result of occlusion, the area supplied by the occluded artery may receive collateral flow from the LC. The LC, therefore, provides flow to its own area plus additional flow to the LAD area so that flow through the LC increases.[14] Second, in our study, occlusion of the LAD resulted in a small increase in heart rate. It is likely that the heart rate change contributed to the increase in flow through the LC. Third, although it was not evaluated in this study, occlusion of the LAD may have resulted in an increased force of contraction in the remaining normally perfused myocardium. Although an initial increase in active shortening of the normal area has been observed after coronary occlusion,[15] this has not always been found.[16] As a result of any or all of these factors, LAD occlusion resulted in a decrease in distal LC resistance and an increase in flow through the normal LC.

In the presence of a severe LC stenosis (Group 1), the results were very different. Occlusion of the LAD resulted in a decrease in flow through the stenotic LC. As

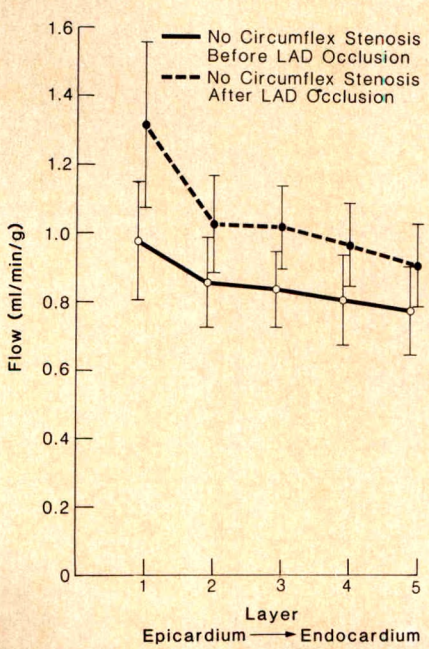

FIGURE 4. Mean left ventricular myocardial blood flow to 5 transmural layers of the posterior papillary muscle region before and after left anterior descending (LAD) coronary artery occlusion in the absence of a circumflex stenosis.

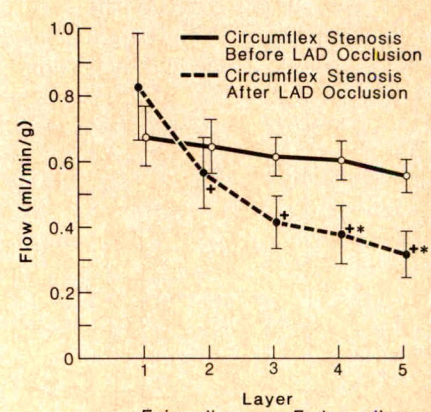

FIGURE 5. Mean left ventricular myocardial blood flow to 5 transmural layers of the posterior papillary muscle region before and after left anterior descending (LAD) coronary artery occlusion in the presence of a circumflex stenosis. * $p < 0.05$ compared with before occlusion; † $p < 0.05$ compared with layer 1.

shown in Table I, there was a decrease in distal LC resistance and an increase in stenosis resistance, suggesting that the increase in the severity of the stenosis led to the decrease in flow through the LC.

The mechanisms responsible for dilation of the distal bed of the stenotic LC in response to LAD occlusion are similar to those just described for the normal LC. In addition, in the presence of an LC stenosis severe enough to produce a pressure gradient, the LAD may have supplied collateral flow to the myocardium in the LC distribution. Occlusion of the LAD would interrupt this collateral flow, perhaps contributing to compensatory dilation of the LC arteriolar bed.

There are two possible explanations for the increased severity of the LC stenosis after LAD occlusion. The first is active constriction of the stenotic segment. Occlusion of the LAD could result in increased sympathetic activity which could possibly result in active constriction of the LC. It has previously been shown, however, that active constriction of an artery with an external snare stenosis has little hemodynamic effect.[17] Therefore, this explanation for the increased severity of the LC stenoses seems unlikely.

The second possible explanation is a passive increase in stenosis resistance. In the presence of LC stenosis, LAD occlusion resulted in dilation of the distal LC bed as evidenced by the decrease in distal LC pressure and the decrease in distal LC resistance. Previous studies have shown that in the presence of a severe coronary stenosis, dilation of the distal coronary bed can result in a decrease in flow through the stenotic coronary artery.[5,6] A similar mechanism may be responsible for the findings in the present study. Occlusion of the LAD resulted in dilation of the distal LC bed and a decrease in distal LC pressure. Pressure in the stenotic segment itself would also be expected to decrease.[18] This decrease in intraluminal pressure may then result in passive narrowing of the stenotic segment. A passive decrease in stenosis caliber could increase stenosis resistance sufficiently to cause a decrease in flow.

It has previously been shown that a decrease in intraluminal pressure leads to an increase in resistance across nonfixed stenoses but not across fixed, rigid stenoses.[19,20] Therefore an increase in stenosis resistance and a decrease in flow through a stenotic coronary artery in response to occlusion of a neighboring coronary artery should occur only if the stenosis is compliant and capable of passively narrowing. It has previously been shown that stenoses produced with external snares are compliant.[20]

The animals in Group 2 differed from the animals in Group 1 in that the stenoses in Group 2 were adjusted so that occlusion of the LAD did not result in a significant change in mean flow through the stenotic LC. Although anterograde flow through the LC did not change, total flow to the area of myocardium supplied by the LC as measured with radioactive microspheres decreased from 0.62 ± 0.02 to 0.50 ± 0.09 ml/min/g ($p < 0.05$). This decrease in regional flow may have been due to the fact that flow through collateral vessels from the LAD to the LC region was cut off by LAD occlusion.

In addition, occlusion of the LAD resulted in a transmural redistribution of blood flow away from the subendocardium in the region supplied by the stenotic LC. There was no significant change in flow to the subepicardial layer and a significant decrease in flow to the subendocardial layers. This redistribution of flow most likely resulted from a combination of several factors. In the presence of a flow-limiting coronary stenosis, the proportion of flow occurring during systole increases.[21] Extravascular compression during systole results in a transmural myocardial flow gradient so that the subendocardial layers are underperfused.[22,23] In addition, dilation of the coronary arteriolar bed distal to the stenosis results in a decrease in coronary pressure distal to the stenosis. Previous studies have suggested that an intramyocardial pressure gradient increasing from subepicardium to subendocardium may exist during diastole.[24] An intrinsic gradient of coronary vascularity may also exist favoring blood flow to the endocardium during diastole.[25] However, in the presence of a flow-limiting coronary stenosis, as pressure distal to the stenosis decreases, vasodilation may occur which limits the ability of the coronary resistance vessels to further dilate and maintain the vascular resistance gradient favoring the subendocardium.[26] In this situation, when the vessels cannot further dilate and the pressure within the vessels is very low, the extravascular tissue pressure may impede subendocardial blood flow.

Left ventricular end-diastolic pressure increased modestly after LAD coronary artery occlusion. It has been shown that an increase in preload selectively reduces flow in the inner layers of the heart, probably because of an increase in intramyocardial tissue pressure.[7,8] In the present study, the increase in left ventricular diastolic pressure may have increased extravascular myocardial tissue pressure, an effect that would be most marked in the subendocardial layers and would further impede subendocardial flow.

LAD occlusion resulted in an increase in heart rate in this portion of the study which averaged 25 beats/min. In the presence of a dilated coronary bed, tachycardia can also result in a redistribution of flow away from the subendocardium.[27] Although the increase in heart rate in the present study was relatively small, it may have contributed to the redistribution of blood flow.

In summary, the present data demonstrate that occlusion of a coronary artery can cause a decrease in flow to the area supplied by a neighboring stenotic artery in 3 ways. First, coronary occlusion may cause a decrease in anterograde flow through the stenotic artery because of a passive increase in stenosis resistance. Second, occlusion of a coronary artery can result in a decrease in subendocardial flow to the area supplied by the neighboring stenotic artery. Finally, it is possible that occlusion of a coronary artery may interrupt collateral flow to the myocardium supplied by a neighboring stenotic artery. All of these mechanisms could potentially cause ischemia distant from an area of total coronary occlusion.

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Roles of the Right Ventricular Free Wall and Ventricular Septum in Right Ventricular Performance and Influence of the Parietal Pericardium During Right Ventricular Failure in Dogs

MASATO TANI, MD

The roles of the right ventricular (RV) free wall and ventricular septum in RV performance were studied in the canine heart. The parietal pericardium was kept intact. Acute ischemia of the RV free wall from right coronary ligation decreased the RV stroke work index more than did that of the ventricular septum from the septal branch of the left coronary artery ligation (41 and 23%, respectively, $p < 0.01$). The response of the RV stroke work index to acute volume loading was also decreased. Left ventricular dysfunction was detected only with ventricular septal ischemia. Combined RV free wall and ventricular septal ischemia produced more severe and predominant RV dysfunction with disproportionate elevation of RV end-diastolic pressure. After combined ischemia, pericardiotomy improved the RV stroke work index as well as the left ventricular stroke work index (40 and 27%, respectively, $p < 0.05$), although the increase in RV stroke work index was greater than in left ventricular stroke work index ($p < 0.05$).

The results of this study suggest that (1) the RV free wall has a more important role than the ventricular septum in RV performance, (2) predominant RV failure can be induced experimentally after combined RV free wall and ventricular septal ischemia, and (3) the pericardium has a restrictive effect on the damaged and dilated right ventricle.

It has been reported that experimental destruction of the right ventricular (RV) free wall does not produce RV failure in the absence of RV overloading.[1–3] In contrast, patients with inferior myocardial infarction may have signs of predominant RV failure, and the ventricular septum (VS) is usually involved in addition to the RV free wall.[4–7] This involvement of the VS may be the major difference between clinical RV infarction and experimental RV destruction. Another difference which could affect RV function is the opened parietal pericardium in previous experiments. Further studies are indicated to clarify the separate roles of the RV free wall, VS, and pericardium in RV performance. In the present study, we attempted (1) to induce RV dysfunction under acute RV free wall and ventricular septal ischemia, (2) to clarify the roles of the RV free wall and VS in RV performance, and (3) to demonstrate the influence of the parietal pericardium on the function of the severely damaged and dilated right ventricle.

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Methods

Fifteen mongrel dogs weighing 15 to 27 kg were anesthetized with pentobarbital (15 mg/kg, intravenously). The dogs were intubated and ventilated with a respirator (Harvard Apparatus). After a median sternotomy and left thoracotomy, the heart was exposed. Two small incisions were made in the pericardium at the base of the aorta for inserting sutures to ligate the right coronary artery, the septal branch of the left coronary artery, or both. The rest of the pericardium was kept intact. Heart rate was kept constant by right atrial pacing at the rate of 120 beats/min after sinoatrial nodal destruction. An electromagnetic flow probe (Nihon Koden) was placed around the root of the aorta through pericardial incisions. Blood pressure in the left ventricle, aorta, right ventricle, and pulmonary artery was measured through fluid-filled catheters and pressure transducers (Statham P23Db). All recordings were performed with an 8-channel recorder (Nihon Koden

WT 685 G). The first derivative of left ventricular (LV) pressure (dP/dt) was obtained continuously by differentiating the LV pressure electrically. A large bore catheter placed in the right atrium was connected to a reservoir filled with blood. Preload on the right ventricle was varied by changing the height of the reservoir. Direct measurement of pulmonary arterial flow with a flow probe is technically difficult, because the pulmonary artery may be easily constricted. Therefore, the LV and RV stroke work indexes were calculated during a steady state using aortic flow. In the left ventricle, ventricular function was also evaluated by LV peak dP/dt at matched levels of LV end-diastolic pressure.

Hemodynamic study: The control recording was obtained at a RV end-diastolic pressure of 4 mm Hg. Then, bilateral ventricular function curves were produced. RV end-diastolic pressure was changed from 3 to 8 mm Hg, while that of LV end-diastolic pressure changed from 3 to 13 mm Hg. Each end-diastolic pressure was kept constant by disconnecting the reservoir for more than 3 minutes to obtain a steady circulatory state before recording each point of the ventricular function curve. After RV end-diastolic pressure was reset at 4 mm Hg, coronary arterial ligation was done. The right coronary artery was occluded in 8 dogs and the septal branch in 7 dogs. Fifteen minutes after ligation, when hemodynamic function was stabilized, recordings at rest and during volume loading were performed using the same procedure.

In the 12 dogs who lived after these procedures, RV end-diastolic pressure was reset at 4 mm Hg and the remaining contralateral coronary artery was occluded. Four dogs died after the second coronary arterial ligation. In the remaining 8 dogs, each variable was recorded in the resting state and the same maneuver for constructing bilateral ventricular function curves was performed.

In the 8 dogs who lived after combined coronary ligation, RV end-diastolic pressure was again reset to the same value as before volume loading, but after combined ligation and with the reservoir disconnected. The parietal pericardium was removed and changes in hemodynamic variables were recorded.

Anatomic study: After completion of the hemodynamic studies, in 13 of 15 dogs the right coronary artery and septal branch were cannulated just distal to the site of ligation. Dyes (different colors of Parker ink) were injected into each vessel manually at a pressure of 100 to 120 mm Hg and the perfusion area was determined. According to Reiner's method, the resected heart was divided into the RV free wall, VS, and LV free wall.[8] Each myocardial mass was weighed.

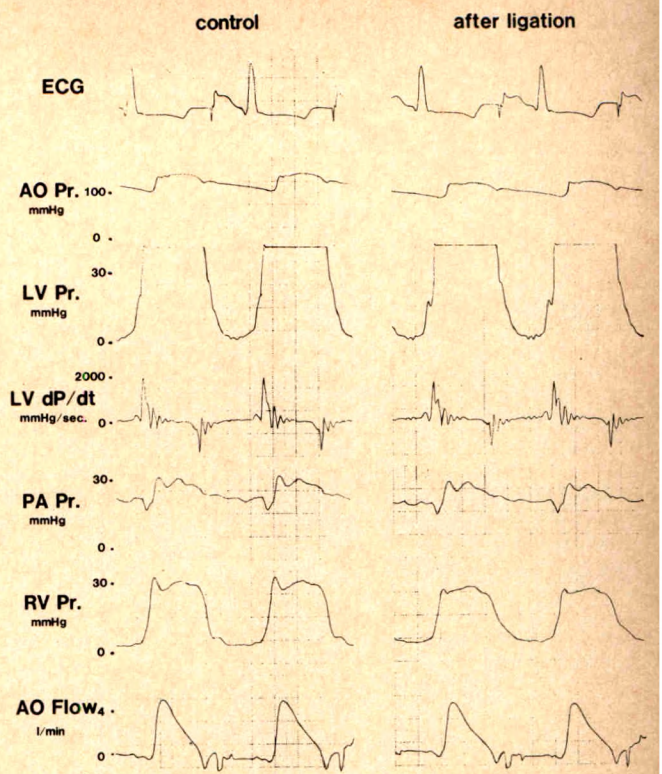

FIGURE 1. Representative hemodynamic changes of the right and left ventricles after right coronary ligation (dog 1). Right ventricular hemodynamic deterioration was observed with decreases in left ventricular end-diastolic pressure, left ventricular systolic pressure, and aortic flow, which could be due to disturbances in left ventricular filling after right coronary ligation. AO Flow = aortic flow; AO P = aortic pressure; ECG = electrocardiogram; LV dP/dt = the first derivative of left ventricular pressure; LV P = left ventricular pressure; PA P = pulmonary arterial pressure; RV P = right ventricular pressure.

Statistical analysis: In each intervention group, the means and standard deviations of the hemodynamic variables were calculated, as were their differences between the control and

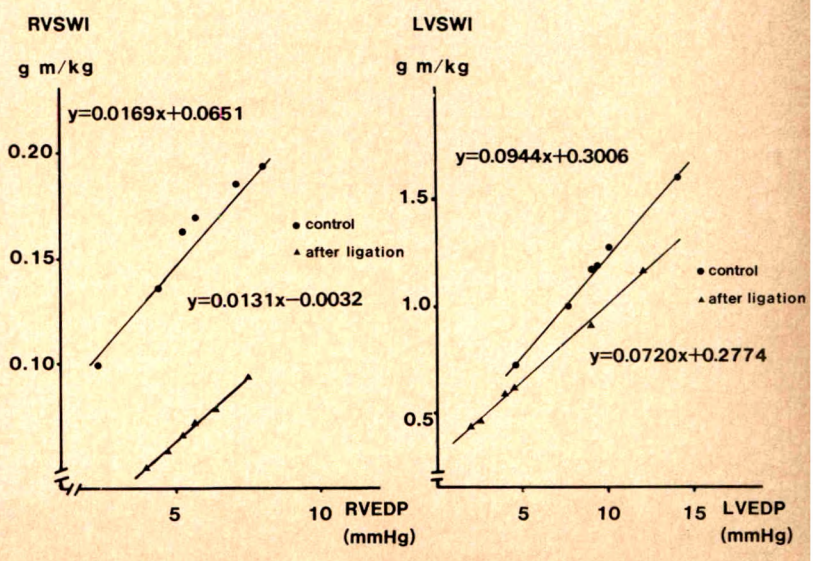

FIGURE 2. Changes in both right and left ventricular function curves after right coronary ligation (dog 2). Both ventricular function curves were noted to be linear before and after right coronary ligation as determined by linear regression analysis. The right ventricular function curve was markedly shifted down to the right. It was also rotated in a clockwise direction. LVEDP = left ventricular end-diastolic pressure; LVSWI = left ventricular stroke work index; RVEDP = right ventricular end-diastolic pressure; RVSWI = right ventricular stroke work index.

TABLE I Effects of Right Ventricular Ischemia

	Control	After Ligation	Difference
Hemodynamic Changes After Right Coronary Ligation (n = 8)			
RVEDP (mm Hg)	4.3 ± 1.1	5.8 ± 1.0	+1.5 ± 0.7*
RVSP (mm Hg)	28 ± 5	25 ± 4	−2.7 ± 1.3†
PA mean (mm Hg)	20 ± 6	17 ± 5	−2.7 ± 1.3†
RVSWI (g·m/kg)	0.224 ± 0.031	0.133 ± 0.058	−40.6 ± 14.6%‡
LVEDP (mm Hg)	6.3 ± 3.1	5.3 ± 3.1	−1.1 ± 0.8†
LVSP (mm Hg)	122 ± 24	111 ± 33	−11.2 ± 11.2§
AO mean (mm Hg)	100 ± 19	93 ± 28	−7.5 ± 10.2§
LVSWI (g·m/kg)	1.378 ± 0.203	1.054 ± 0.099	−23.5 ± 12.6%*
LV peak dP/dt (mm Hg/s) (LVEDP = 6 mm Hg)	1,678 ± 662	1,797 ± 931¶	. . .
Increase in Stroke Work Indexes in Response to Volume Loading (n = 8)			
RVSWI in RVEDP at 3 mm Hg (g·m/kg)	0.196 ± 0.040	0.115 ± 0.049	. . .
RVSWI in RVEDP at 8 mm Hg (g·m/kg)	0.335 ± 0.063	0.175 ± 0.078	. . .
Increase in RVSWI (g·m/kg)	0.136 ± 0.074	0.060 ± 0.034*	. . .
LVSWI in LVEDP at 3 mm Hg (g·m/kg)	1.055 ± 0.221	0.765 ± 0.140	. . .
LVSWI in LVEDP at 13 mm Hg (g·m/kg)	2.133 ± 0.373	1.730 ± 0.241	. . .
Increase in LVSWI (g·m/kg)	1.077 ± 0.406	0.966 ± 0.320¶	. . .
Changes in Curve of Relation Between LV and RV End-Diastolic Pressure (n = 8)			
Slope (mm Hg/mm Hg)	0.509 ± 0.299	0.768 ± 0.277*	. . .
Intercept (mm Hg) (RVEDP in LVEDP at 0 mm Hg)	1.403 ± 2.735	2.210 ± 2.935¶	. . .

* $p < 0.01$.
† $p < 0.02$.
‡ $p < 0.001$.
§ $p < 0.05$.
¶ not significant versus control.
AO mean = mean aortic pressure; LVEDP = left ventricular end-diastolic pressure; LV peak dP/dt = peak value of the first derivative of the left ventricular stroke work index; PA mean = mean pulmonary arterial pressure; RVEDP = right ventricular end-diastolic pressure; RVSP = right ventricular systolic pressure; RVSWI = right ventricular stroke work index.

TABLE II Effects of Ventricular Septal Ischemia

	Control	After Ligation	Difference
Hemodynamic Changes After Septal Branch of the Left Coronary Artery Ligation (n = 7)			
RVEDP (mm Hg)	3.8 ± 1.0	4.9 ± 1.1	+1.0 ± 0.5*
RVSP (mm Hg)	31 ± 9	29 ± 9	−1.9 ± 1.2†
PA mean (mm Hg)	20 ± 4	19 ± 5	−0.4 ± 0.5‡
RVSWI (g·m/kg)	0.206 ± 0.057	0.154 ± 0.038	−23.4 ± 14.6%†
LVEDP (mm Hg)	4.9 ± 0.9	6.0 ± 0.7	+1.1 ± 0.5§
LVSP (mm Hg)	122 ± 24	120 ± 22	−2.0 ± 2.3¶
AO mean (mm Hg)	103 ± 16	99 ± 13	−3.5 ± 3.3¶
LVSWI (g·m/kg)	1.269 ± 0.107	0.998 ± 0.169	−21.4 ± 13.5%*
LV peak dP/dt (mm Hg/s) (LVEDP = 6 mm Hg)	2,317 ± 542	1,648 ± 172*	. . .
Increase in Stroke Work Indexes in Response to Volume Loading (n = 7)			
RVSWI in RVEDF at 3 mm Hg (g·m/kg)	0.16 ± 0.070	0.126 ± 0.071	. . .
RVSWI in RVEDP at 8 mm Hg (g·m/kg)	0.318 ± 0.043	0.263 ± 0.050	. . .
Increase in RVSWI (g·m/kg)	0.157 ± 0.084	0.137 ± 0.090¶	. . .
LVSWI in LVEDP at 3 mm Hg (g·m/kg)	0.961 ± 0.200	0.734 ± 0.209	. . .
LVSWI in LVEDP at 13 mm Hg (g·m/kg)	1.986 ± 0.231	1.616 ± 0.175	. . .
Increase in LVSWI (g·m/kg)	1.024 ± 0.394	0.882 ± 0.246**	. . .
Changes in Curve of Relation Between LV and RV End-Diastolic Pressure (n = 7)			
Slope (mm Hg/mm Hg)	0.598 ± 0.212	0.628 ± 0.268‡	. . .
Intercept (mm Hg) (RVEDP in LVEDP at 0 mm Hg)	0.901 ± 2.328	1.119 ± 3.282‡	. . .

* $p < 0.01$.
† $p < 0.02$.
‡ not significant.
§ $p < 0.001$.
¶ $p < 0.05$.
** $0.05 < p < 0.1$ versus control.
Abbreviations as in Table I.

intervention periods. Ventricular end-diastolic pressure-stroke work index relations and the relations between LV and RV end-diastolic pressure were fitted to linear or exponential regression lines ($y = a \cdot x + b$ or $y = a \cdot b^x + c$) using the least-squares methods. Increases in stroke work indexes between given end-diastolic pressures were calculated by these regression lines and their means and standard deviations were used for statistical analysis. Hemodynamic changes with each intervention were analyzed by a paired t test of $n - 2$ degrees of freedom. An unpaired t test of $n - 1$ degree of freedom was performed for comparison of 2 groups.

Results

Hemodynamic study: *Right coronary ligation:* Representative tracings from dog 1 are shown in Figure 1. Right coronary ligation increased the mean value of RV end-diastolic pressure by 1.5 mm Hg, while RV systolic pressure was decreased. The LV stroke work index was reduced, but its percent reduction was less than that in the right-ventricle ($p < 0.01$). LV peak dP/dt did not change (Table I). In each dog, RV and LV function curves were constructed. Right coronary ligation shifted the RV function curve down more than that in the left ventricle to the right (Fig. 2) (dog 2). The increases in stroke work index decreased only in the right ventricle (Table I). The relationship between LV and RV end-diastolic pressure was linear before and after ligation (Fig. 3) (dog 3). Their slopes increased, although their intercepts did not change. (Table I). In the 2 dogs, the RV stroke work index was reduced 50% in the resting state; they died with acute hemodynamic deterioration when preload to the right ventricle was decreased after volume loading.

Septal branch of the left coronary artery ligation: Septal branch ligation increased the mean value of RV and LV end-diastolic pressures with decreases in RV and LV stroke work index to the same extent (Table II). The reduction in the RV stroke work index induced by septal branch ligation was less than that induced by right coronary ligation ($p < 0.05$). After septal branch ligation, not only the RV but also the LV function curves shifted to the right; however, both remained linear. Changes in increases of the stroke work indexes in response to volume loading were reduced only in the right ventricle (Table II). The relationship between LV and RV end-diastolic pressures was linear before and after septal branch ligation. Their slopes and intercepts were not changed (Table II). One dog (dog 9) died with hypotension due to fatal arrhythmia during preload reduction to the right ventricle after volume loading.

Combined right coronary and septal branch ligation: In the 12 dogs with right coronary or septal branch ligation, the contralateral coronary artery was occluded after resetting of RV end-diastolic pressure at 4 mm Hg. Two dogs died with fatal arrhythmias. Two others (dogs 6 and 7) in which the RV stroke work index had already been reduced >50% after right coronary ligation died with hemodynamic deterioration after additional septal branch ligation. In 1 of these 2 (dog 7), RV end-diastolic pressure increased up to 12 mm Hg with decrease in RV systolic pressure and cardiac output, although LV end-diastolic pressure stayed within normal range (Fig. 4).

In the 8 dogs that survived combined coronary ligation, the mean value of RV end-diastolic pressure increased 1.9 mm Hg. The RV stroke work index was reduced by 55% with a decrease in the mean value of RV systolic pressure. Combined ligation increased LV end-diastolic pressure, although its increase was less than that in the right ventricle and it remained within

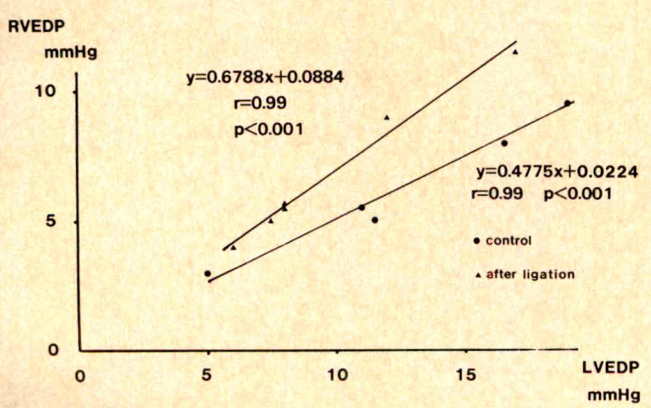

FIGURE 3. Changes in the relationship between left and right ventricular end-diastolic pressure after right coronary ligation (dog 3). The relation between left and right ventricular end-diastolic pressure was linear before and after right coronary ligation. The regression line shifted up and its slope became steeper after right coronary ligation. Abbreviations as in Figure 2.

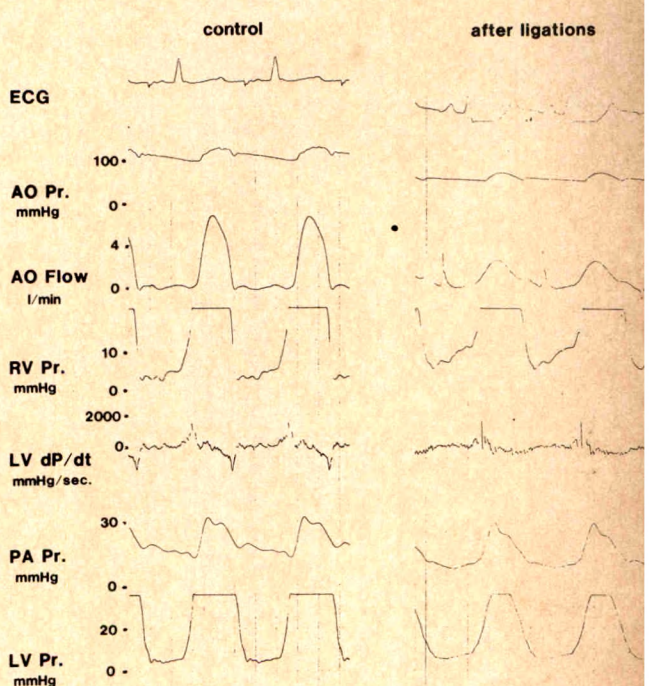

FIGURE 4. Hemodynamic changes in the right and left ventricles after combined right coronary and septal branch of the left coronary artery ligation (dog 7). Right ventricular end-diastolic pressure increased disproportionately compared with left ventricular end-diastolic pressure, which means predominant right ventricular failure. Abbreviations as in Figure 1.

TABLE III Effects of Right Ventricular and Ventricular Septal Ischemia

	Control	After Combined Ligation	Difference
Hemodynamic Changes After Combined Ligation of Right Coronary Artery and Septal Branch of the Left Coronary Artery (n = 8)			
RVEDP (mm Hg)	4.1 ± 1.0	6.0 ± 1.1	+2.0 ± 0.9*
RVSP (mm Hg)	31 ± 8	26 ± 7	−5.1 ± 2.9†
PA mean (mm Hg)	20 ± 4	15 ± 3	−5.3 ± 1.7‡
RVSWI (g·m/kg)	0.207 ± 0.063	0.094 ± 0.042	−54.6 ± 12.3%*
LVEDP (mm Hg)	5.0 ± 1.5	6.0 ± 1.5	+1.0 ± 0.8†
LVSP (mm Hg)	119 ± 22	99 ± 20	−20.1 ± 12.0†
AO mean (mm Hg)	98 ± 17	80 ± 16	−17.9 ± 12.5‡
LVSWI (g·m/kg)	1.221 ± 0.075	0.815 ± 0.117	−33.2 ± 13.7%‡
Increase in Stroke Work Indexes in Response to Volume Loading (n = 8)			
RVSWI in RVEDP at 3 mm Hg (g·m/kg)	0.178 ± 0.036	0.084 ± 0.033	. . .
RVSWI in RVEDP at 8 mm Hg (g·m/kg)	0.328 ± 0.088	0.163 ± 0.047	. . .
Increase in RVSWI (g·m/kg)	0.151 ± 0.066	0.079 ± 0.041*	. . .
LVSWI in LVEDP at 3 mm Hg (g·m/kg)	1.165 ± 0.296	0.730 ± 0.282	. . .
LVSWI in LVEDP at 13 mm Hg (g·m/kg)	2.031 ± 0.363	1.544 ± 0.268	. . .
Increase in LVSWI (g·m/kg)	0.866 ± 0.303	0.814 ± 0.288§	. . .
Changes in Curve of Relation Between LV and RV End-Diastolic Pressure (n = 8)			
Slope (mm Hg/ mm Hg)	0.474 ± 0.167	0.781 ± 0.266¶	. . .
Intercept (mm Hg) (RVEDP in LVEDP at 0 mm Hg)	0.580 ± 2.196	0.898 ± 3.231§	. . .

* $p < 0.001$.
† $p < 0.02$.
‡ $p < 0.01$.
§ not significant.
¶ $p < 0.05$ versus control.
Abbreviations as in Table I.

normal range ($p < 0.05$). The LV stroke work index reduced, but this reduction was less than that in the right ventricle ($p < 0.01$, Table III).

The RV and LV function curves after combined ligation were depressed and became curvilinear. One such pair is presented in Figure 5 (dog 10). Changes in increases of the stroke work indexes in response to volume loading were reduced, especially in the right ventricle ($p < 0.05$, Table III).

Effect of pericardiotomy after combined coronary ligation: Pericardiotomy decreased RV and LV end-diastolic pressure, although hemodynamic function improved. Increase in the RV stroke work index at rest after pericardiotomy was more than that in the left ventricle ($p < 0.05$) (Table IV).

Anatomic study: The weight of the RV free wall was 27 ± 2% of both ventricles and 52 ± 4% of the right ventricle (RV free wall + VS). The VS was 26 ± 3% of

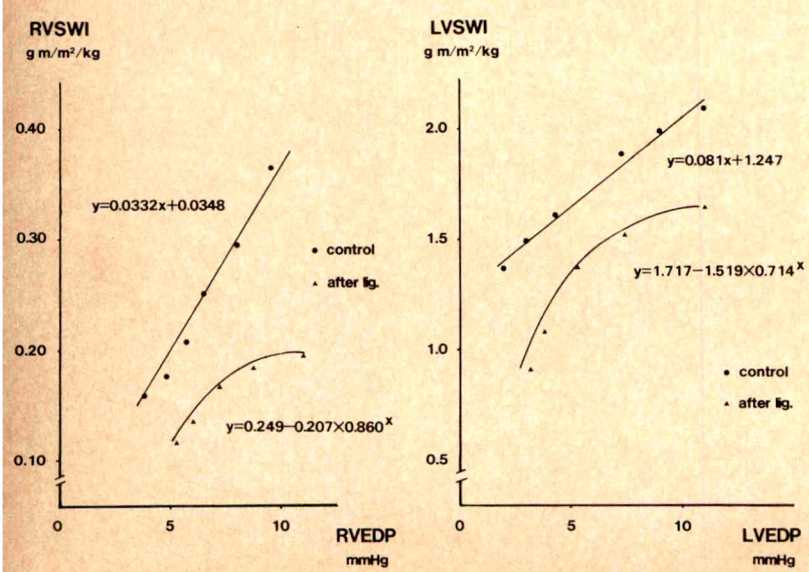

FIGURE 5. Changes in ventricular function curves after combined right coronary and septal branch of the left coronary artery ligation (dog 10). Biventricular function curves were linear before combined ligation of the right coronary artery and septal branch of the left coronary artery. After ligation, they became curvilinear and exhibited a plateau at high end-distolic pressures. They were described by exponential regression analysis ($y = a \cdot b^x + c$). Abbreviations as in Figure 2.

TABLE IV Hemodynamic Changes After Pericardiotomy in Cases With Combined Ligation (n = 8)

	Before	After Pericardiotomy	Difference
RVEDP (mm Hg)	6.1 ± 1.0	4.5 ± 0.5	−1.6 ± 0.5*
RVSP (mm Hg)	27 ± 7	29 ± 6	+2.3 ± 2.5†
PA mean (mm Hg)	17 ± 3	18 ± 4	+1.3 ± 1.4†
RVSWI (g·m/kg)	0.110 ± 0.058	0.154 ± 0.070	+40.3 ± 33.2%‡
LVEDP (mm Hg)	6.2 ± 1.5	4.6 ± 1.6	−1.4 ± 0.8§
LVSP (mm Hg)	98 ± 18	107 ± 16	+11.4 ± 10.2‡
AO mean (mm Hg)	81 ± 14	91 ± 14	+10.3 ± 10.2§
LVSWI (g·m/kg)	0.777 ± 0.109	0.986 ± 0.204	+27.2 ± 24.8%†

* $p < 0.001$.
† $p < 0.05$.
‡ $p < 0.02$.
§ $p < 0.01$ versus before pericardiotomy.
Abbreviations as in Table I.

both ventricles and 48 ± 4% of the right ventricle. The right coronary artery perfused 77 ± 7% of the RV free wall and 41 ± 4% of the right ventricle by weight. The right coronary artery did not perfuse the LV free wall. The septal branch supplied blood to 76 ± 11% of the VS and 37 ± 3% of the right ventricle by weight. The perfusion area of the septal branch was 26 ± 2% of the left ventricle (LV free wall + VS), but showed no perfusion area in the LV free wall or in the RV free wall. There was no difference between the perfusion area of the right coronary artery and that of the septal branch in the right ventricle.

Discussion

Clinical RV infarction can be recognized by disproportionately high RV end-diastolic pressure compared with LV end-diastolic pressure with or without a restrictive pressure pattern of the right ventricle.[4,9–14] In almost all the cases of RV infarction, the RV free wall and the posterior one third of the VS have been involved.[7] On the other hand, it has been reported that RV failure could not be produced in animal experiments in which the RV free wall only had been destroyed with the opened parietal pericardium.[1–3] These clinical and experimental observations suggest that contraction of the VS plays a role in RV pump function, and the parietal pericardium modifies RV performance.

In the present experiment, ischemia in RV free wall with the pericardium intact decreased the RV stroke work index >40%. These data are consistent with those of Goldstein et al.[15] They reported that the damage to the RV free wall reduced not only the RV stroke work index, but also that in the left ventricle by >60%. In their experiment, RV end-diastolic pressure was in the upper normal range initially, which may mean preexisting high preload to the right ventricle. Fixler et al[16] reported that the RV function curve during acute volume loading depressed after right coronary ligation which reduced RV myocardial blood flow by 40%, while that of the left ventricle did not shift. The shift of the function curve to the right and the reduction in the increase of the RV stroke work index to volume loading after right coronary ligation in our study are consistent with those in previous reports.

There have been a few reports that elevation of the filling pressure of 1 ventricle changed the pressure-volume relation and the function curve in the contralateral ventricle. The overloading of the right ventricle induced distortion of LV geometry and disturbed its filling under a given LV filling pressure. The existence of the intact pericardium enhanced these interactions.[17–21] In our study, the rightward shift of the LV function curve without any decrease in LV peak dP/dt and increase in LV stroke work index after right coronary ligation was observed. It does not mean real LV dysfunction and is mainly due to direct interaction from the damaged right ventricle. The upward shift in the LV and RV end-diastolic pressure relation suggested that the compliance of the right ventricle may be reduced more than that of the left ventricle and that pressure-volume relations in both ventricles may be altered by direct interaction between them.

There have been few reports on the role of the VS in RV function. Brooks et al[22] studied the effects of ischemia of the anterolateral, anteroseptal, or inferoseptal wall of the left ventricle on both ventricular functions in pigs, whose coronary system is similar to that of human beings. RV function was depressed only by the inferoseptal and anteroseptal ischemia. This finding suggests that the contraction of the VS makes some contribution to maintaining RV function. Fixler et al[16] produced selective ischemia in the VS in dogs by septal branch ligation, which reduced its blood flow >40% and reported that RV function was depressed without any depression of LV function. The fact that LV peak dP/dt was decreased in our study could be evidence of an LV contraction abnormality induced by septal branch ligation. No significant change in LV and RV end-diastolic pressure relation suggested that the compliance of each ventricle was affected to the same extent.

It has not been previously reported that the VS and RV free wall were destroyed at the same time and that predominant RV failure could be produced experimentally. We were able to produce predominant RV failure with combined right coronary and septal branch ligation, demonstrating the contribution of contraction of the RV free wall and VS to RV function (Fig. 4).

Santamore et al[23] reported that RV pressure development might depend mainly on the contraction of the left ventricle, although Goldstein et al[15] stated the importance of the RV free wall. In our study, RV systolic pressure was decreased moderately after the destruction of the RV free wall, the VS, or both. It can be stated that their contraction plays an important role in ejection of blood from the right ventricle but not so much in the development of RV pressure.

Clinical or hemodynamic signs of RV infarction have been reported to improve or disappear within several days after onset.[9–11] The left ventricle dilates to compensate for the decreased ejection fraction and improves stroke volume. The existence of the same mechanism in the damaged right ventricle has already been suggested in clinical reports.[24,25] We can presume that the pressure pattern in RV infarction is caused by the restrictive effect of the pericardium on the dilating right ventricle. It was suggested that the right ventricle dilated after the destruction of the RV free wall, although the left ventricle might be distorted and its volume might be decreased, even at the same filling pressure with the pericardium intact.[15] Hemodynamic improvement in RV performance after pericardiotomy supports the existence of such a restrictive mechanism.

It has been said that volume loading is effective for the low output state found in clinical RV infarction. The present study suggests that in clinical RV infarction, not only volume expansion but also pericardiotomy improves such a decrease in cardiac output without worsening of pulmonary congestion, even in cases with combined LV dysfunction, although the latter might not be practical in the acute stage of RV infarction. It is presumed that pericardial distension after the acute stage may cause hemodynamic improvement and disappearance of a restrictive pressure pattern in the right ventricle in clinical situations.

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Effect of Fluocarbon Exchange Transfusion on Myocardial Infarction Size in Dogs

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Fluosol DA (20%), a perfluocarbon with high oxygen solubility, was administered by concurrent exchange transfusion (30 ml/kg) to anesthetized open-chested adult greyhounds (n = 9) 1 hour after left anterior descending coronary ligation. Mechanical ventilation using 100% oxygen was used throughout the experiment. A second similar group (n = 9) received 0.9% normal saline solution (30 ml/kg), and a third group (n = 9) received no further intervention. Systemic, right atrial, and left atrial pressures were not altered by the exchange transfusion. Monastryl blue dye was injected through the left atrial line at 6 hours after ligation to define the area of myocardium at risk (A_R); the animals were then killed and the heart was excised. The left ventricle was sliced at 5 mm intervals and stained using triphenyltetrazolium chloride, defining areas of necrosis (A_N). The ratio of A_N/A_R and total left ventricular mass were then compared with the use of planimetry.

The results were as follows: the A_N/A_R ratio in the 9 control animals was 90 ± 2 (mean ± standard error of the mean); in the 9 animals who received saline solution it was 88 ± 2; and in the animals who received Fluosol it was 67 ± 4 ($p < 0.01$ compared with control; $p < 0.001$ compared with the saline group).

Fluocarbon exchange transfusion may reduce infarct size when administered after coronary occlusion.

After coronary occlusion, the total mass of myocardium infarcted is an important determinant of morbidity and mortality.[1–3] The extent of myocardial necrosis is not necessarily predetermined at the time of coronary occlusion, but rather a central area of inevitably necrotic tissue is surrounded by a zone of threatened but potentially salvageable ischemic myocardium.[4–7] Several agents have been shown to be beneficial in reducing the ultimate area of myocardial infarction (AMI) when applied during the period of myocardial ischemia.[8–12] The role of oxygen therapy in the management of AMI has been well explored,[13–15] and fluocarbons with extremely high oxygen solubility have been shown to act as effective agents of oxygen transport.[16–20] There has been speculation that these agents may provide beneficial effects to ischemic myocardium because their small particle size allows penetration of edematous vessels occurring as part of the "no reflow" phenomena,[21] and because of their ability to carry oxygen in physical solution, to release oxygen to tissues at low tissue partial pressure of oxygen[22] and their ability to transport carbon dioxide away from ischemic, acidotic tissues functioning under conditions of anaerobic metabolism.

This study was designed to evaluate the effect of Fluosol DA (20%) on the area of AMI, given as a partial exchange transfusion 1 hour after acute coronary occlusion in the dog and evaluated 6 hours after onset of ischemia.

Methods

Adult retired racing greyhounds, weighing 22 to 32 kg (mean 26.5) were anesthetized with sodium thiopental (30 mg/kg intravenously); anesthesia was maintained using chloralose-urethane (6.67 g of chloralose and 80 mg of urethane in 500 ml of 0.9% normal saline solution) given in divided doses of 0.5 ml/kg as required.

All animals were intubated and ventilated with 100% oxygen using a model 607 Harvard respirator, semiclosed circuit,

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TABLE I Arterial Gas Concentration

	Before Exchange Transfusion				Immediately After Exchange Transfusion			
	pO_2	pH	pCO_2	Hct	pO_2	pH	pCO_2	Hct
Group I: control	471	7.51	30	50	...	...	...	...
Group II: saline solution	498	7.57	23	48	555	7.48	25	37
Group III: Fluosol	417	7.52	30	48	432	7.50	33	33

Hct = hematocrit; pCO_2 and pO_2 = partial pressure of carbon dioxide and oxygen, respectively.

TABLE II Areas of Necrosis and Risk

	n	A_N/A_R	A_R/Total Left Ventricle
Group I: control	9	90(56–97) ± 2	23(12–31) ± 2
Group II: saline solution	9	88(80–99) ± 2	18(10–29) ± 2
Group III: Fluosol	9	67(42–80) ± 4*	22(14–30) ± 2†

* A_N/A_R = III versus I, $p < 0.01$; III versus II, $p < 0.001$.
† Difference not significant.
A_N = area of necrosis; A_R = area at risk.
Values given are mean percent ± standard error of the mean. Numbers in parentheses represent the range for each group.

and in-line carbon dioxide absorption. Femoral arterial and venous lines were established and median sternotomy was performed. Systemic arterial and left arterial pressures (through a left atrial appendage catheter) were continuously monitored, together with electrocardiogram, temperature (esophageal), arterial blood gases, and right arterial pressures. Animals were pretreated with procainamide, 500 to 700 mg (20 mg/kg intravenously), 20 minutes before left anterior descending (LAD) coronary artery ligation and thereafter at a rate of 100 mg hourly. In addition, xylocaine (100 mg intravenously and 100 mg topically to the heart) was given at the time of occlusion and subsequently as arrhythmias occurred.

The LAD artery was isolated and snared using a silicone elastomer tape approximately at its midpoint, the actual position being determined by the size and distribution of its diagonal branches. Occlusion at this point produced an area of ischemia of 10 to 25% of the left ventricular mass. The occlusion of the LAD artery was maintained for 6 hours at which time monastryl blue dye (Dupont B.W. 372-P Phthalo-Blue B) was injected into the left atrium and distributed to the nonischemic myocardium at physiologic pressures. The dogs were then killed and the heart quickly excised and sectioned. The left ventricle was isolated from the atria and right ventricles and then cross-sectioned at 5 mm intervals. The left ventricular slices were incubated in triphenyltetrazolium chloride (TTC) for 7 minutes at 35°C. The slices were then placed between 2 glass plates and tracings were made on celluloid sheets. The viable myocardium within the non–monastryl-blue-stained area at risk could be determined by the red stain imparted by TTC in the presence of lactate dehydrogenase. Thus, an area of necrosis (A_N), an area at risk (A_R), and the total left ventricular area for each slice could be defined by planimetry. The ratios of A_N/A_R and A_R to left ventricular mass (A_R/total) were then calculated and compared.

Study groups: Three groups, each with 9 animals, were randomly assembled using 1 of 3 protocols. In Group I, 6-hour ligation of the LAD artery was done without further intervention apart from the maintenance of normal body temperature (Multi-Heat 81 type WP automatic electric heating pad), pH, partial pressure of carbon dioxide (IL Instrumentation Lab Micro 13), and the treatment of arrhythmias. In Group II, a 30 ml/kg 0.9% normal saline solution exchange transfusion was begun; 1 hour after LAD artery ligation the exchange was done in 100 ml aliquots from the central venous line. By this method, there was no change in left atrial or systemic pressure. Group III received Fluosol DA (20%) 1 hour after LAD artery ligation by a similar method of exchange (30 ml/kg). All animals were followed for 6 hours and killed, and the hearts were treated as described previously.

Results

The results are summarized in Tables I and II. There was high arterial partial pressure of oxygen in all 3 groups, and this was maintained throughout the procedures. Arterial blood gases and hematocrit before and after exchange transfusion are shown in Table I. No significant alteration occurred in any of these measurements except the hematocrit level in the exchange groups. There were no significant changes in systemic arterial and left ventricular filling pressures before and after exchange at death in all experimental groups.

Table II shows the ratios of A_N/A_R and A_R/total left ventricle. The mean area at risk was 24, 18, and 22% in the 3 respective groups (difference not significant). The A_N/A_R ratio was significantly different in the Fluosol exchange group compared with the control group ($p < 0.01$) and saline solution exchange ($p < 0.001$).

Discussion

The results of this study demonstrated that the administration of Fluosol DA (20%) 1 hour after the acute coronary occlusion significantly decreased the AMI seen at 6 hours when compared with similarly managed but untreated control dogs, or with saline exchange transfusion. These findings are in accordance with those of Glogar et al,[3] who administered 40 ml/kg of fluocarbon and evaluated the A_R by autoradiography in a pretreatment model. They differ, however, from our experiment in that ours is a clinical treatment model of AMI with therapy begun after the event, whereas in their experiment the exchange transfusion with Fluosol was performed before ligation of the LAD artery. Although the mechanism of Fluosol DA (20%) protection was not elicited in this experiment, it is postulated that the protection of the heart was by high arterial oxygen saturation in and around the ischemic area. Fluocarbons may increase oxygen delivery to ischemic myocardium because their oxygen-carrying capacity at high partial pressure of oxygen is actually superior to blood oxygen (39.4 ml/100 ml of Fluosol versus 20 ml of oxygen/100 ml of blood).[23] The decreased viscosity or small size particles (<0.1 μm) of Fluosol probably improves distribution of oxygen to the myocardium at risk. Rude et al[24] documented increased delivery of oxygen by Fluosol DA to ischemic myocardium by measuring increases in intramyocardial partial pressure of oxygen with a mass

spectrophotometer. This increase was shown with fluocarbon with a mass spectrophotometer. This increase was shown with fluocarbon but not with oxygen alone.[24] We believe that hemodilution per se is not responsible since moderate saline hemodilution did not alter A_N/A_R over controls with normal hematocrit, and previous work has shown no added benefit of hemodilution to infarct size reduction.[25,26]

In this study, an animal model was used that simulated the clinical findings of acute myocardial ischemia progressing to necrosis. The techniques of defining A_R and A_N have previously been shown to be reliable methods of defining areas in which regional myocardial blood flow is <0.4 ml/min/g of tissue and correlate with microscopic and electron microscopic analyses of necrotic tissue and other methods of defining area of risk, such as autoradiography.[23,27,28] The TTC vital staining technique has been well validated both clinically and experimentally as a marker of necrosis as early as 4 hours after occlusion.[28–30]

Myocardial necrosis is a time-related process, and interventions such as Fluosol DA administration that may modify this sequence and result in reduced necrosis within the ischemic area may have important implications in clinical practice in the treatment of acute myocardial infarction.

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EDITORIAL

Fibronectin: Cardiovascular Aspects of a Ubiquitous Glycoprotein

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Our concepts of cardiovascular physiology and disease are largely founded on macroscopic observations of the mechanical and structural state of the heart and vessels. This knowledge is augmented by recent studies of cellular receptors, electrophysiologic features, contractile proteins, and myocardial metabolism. At the level of cellular function, the cardiovascular system remains relatively unexplored. Interactions between cells may determine the morphogenesis and homeostasis of tissue, as well as the response of tissue to increased functional demand or injury. In this editorial, we focus upon the actions of fibronectin, an extracellular glycoprotein, in modulating cellular interactions in the cardiovascular system. We present several potential roles for fibronectin in cardiovascular function and dysfunction which, although lacking immediate therapeutic implications, prompt the interest and speculation of the cardiologist.

Fibronectin is a major cell surface glycoprotein distributed widely in the extracellular matrix of mesenchymal tissues and present in soluble form in the plasma.[1–4] It has been shown to facilitate a vast array of cell processes, including formation of intercellular contacts, adhesion and spreading of cells on substrata, and mediation of cell differentiation and tissue morphogenesis. The tissue distribution and the molecular and cellular actions of fibronectin are applicable to the embryogenesis of the heart and vasculature, the physiology of the blood vessel, and mechanisms of arteriosclerosis. thrombus organization, and myocardial healing after infarction.

Molecular Structure

Plasma and tissue fibronectins have only minor biochemical[5] differences. The basic 220,000 dalton molecular weight subunit occurs most commonly in dimer form in the plasma[6] and also as higher molecular weight disulfide-linked polymers when associated with cells[7] (Fig. 1). Fibronectin is comprised of approximately 5% carbohydrate, which may serve to resist proteolysis of the macromolecule.[8] Intrachain disulfide bonds occur in the polypeptide portion of the molecule. Free sulfhydryl groups are also present and appear to be required for binding of fibronectin to the cell surface.[9]

Tissue and Cellular Distribution

Immunofluorescent studies with antifibronectin antibody have delineated the tissue and cellular distribution of fibronectin. As a major component of the extracellular matrix, fibronectin is extensively distributed in fibrillar form in basement membranes of vessels and capillaries, around smooth muscle cells, at the sarcolemma of striated muscle, and in loose connective tissue.[10,11] It is topographically associated with elastic fibers in the internal and external elastic lamina of large vessels.[12] Complete studies of the distribution of fibronectin in the heart have not been performed. Fibronectin is synthesized in vitro by several cell types, including fibroblasts,[13] endothelial cells,[14] smooth muscle cells,[15] and myoblasts.[16] In tissue culture, fibronectin appears as a fibrillar network between cells and the substratum, between cells at points of intercellular contact, and on the apical cell surface. This distribution varies with cell type, culture conditions, and stage of differentiation and growth.

Cardiovascular Morphogenesis

The ability of fibronectin to induce cell migration and intercellular contact in vitro implies a possible role during embryogenesis. In the chick embryo area vasculosa, fibronectin is concentrated under the epiblast at the leading edge of migrating vascular mesenchyme.[17] Myoblasts require fibronectin for attachment and elongation upon a gelatin-coated substrate and align themselves along oriented fibrils and streaks of fibronectin.[18] Observations of chick embryo heart tissue in organ culture suggest that fibronectin dominates the associative behavior of ventricular tissue.[19] Apposition of 2 dissimilar tissues in organ culture consistently leads to spreading of 1 tissue type over the other. When ventricular myocyte aggregates of different ages are apposed, the aggregate segregating to an internal position displays more surface fibronectin than the aggregate that spreads to an external position. In fetal rat hearts,

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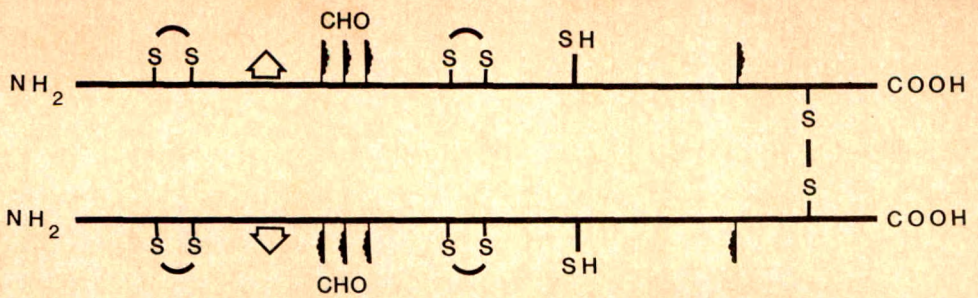

FIGURE 1. Simplified structural model of fibronectin in dimer form. Two polypeptide chains are joined near the carboxy-terminal ends. Inter- and intrachain disulfide bridges (S-S), free sulfhydryl groups (SH), carbohydrate residues (CHO), and the binding sites for collagen and fibrin (**open arrows**) are depicted. (Adapted from Hayashi and Yamada[5] and Wagner and Hynes.[9])

immunofluorescent localization of fibronectin is particularly prominent at the crest of the developing interventricular septum.[20] Thus, fibronectin is present in the developing heart, probably is synthesized by cardiac mesenchyme, and may contribute to formation of the important septal region and other facets of cardiac and vascular structure.

Endothelium and Subendothelium

Endothelial cells provide a selective barrier and a site of active transport between the blood and tissues and maintain this vascular interface by the repair processes of cell proliferation and migration.[21] Fibronectin synthesized by cultured endothelial cells is laid down as a dense fibrillar network beneath the cell monolayer. With disruption of the endothelial lining of the blood vessel, fibronectin in the subendothelial matrix may contribute to adhesion of blood elements[22] and thrombogenesis.[23] Fibronectin may also facilitate migration of endothelial cells for repair of vessel injury and neovascularization. Certain endothelial cells identified in culture secrete fibronectin as they migrate, leaving a continuous trail of the glycoprotein.[24] When these migratory endothelial cells and previously stationary cells are combined in culture, the previously sedentary cells closely follow the path of the migrating cells. Fibronectin may thus serve as a transducer of signals for endothelial cell movement.

As a selective barrier, the endothelium must mediate translocation of leukocytes across the vessel wall. Adherence of granulocytes to the endothelium in vivo precedes their entry into tissue. Recent investigations with radioiodinated plasma fibronectin indicate that monolayer endothelial cells bind large numbers of exogenous fibronectin molecules with strong avidity.[25] Immunofluorescent studies reveal an initial diffuse distribution of exogenous fibronectin on the surface of endothelial cells followed by delayed apical aggregation of the glycoprotein. This surface modulation correlates with the ability of fibronectin to facilitate adhesion of polymorphonuclear granulocytes to the endothelial monolayer.[26]

Atherosclerosis

The strategic location of fibronectin in the arterial wall and its involvement in cell interactions and migration suggest a role in the pathogenesis of atherosclerosis. This possibility has been studied by Stenman et al,[27] who have observed prominent immunofluorescent staining for fibronectin in early cellular atherosclerotic lesions of human muscular arteries.[27] In advanced sclerotic plaques, diffuse staining for fibronectin remains but is less intense. Arterial injury has been proposed as the common precursor of intimal plaque formation.[28] At sites of injury, fibronectin may provide an extracellular matrix which directs cellular invasion either for appropriate tissue repair or for the accumulation of smooth muscle cells and other elements culminating in the atherosclerotic plaque.

Thrombus Organization and Myocardial Healing After Infarction

A significant quantity of fibronectin becomes incorporated into fresh thrombus, as the serum concentration is 20 to 50% less than the plasma concentration.[29] Fibronectin binds to fibrin during clot formation and becomes covalently cross-linked to fibrin. Cross-linking of fibronectin to fibrin on a fibrin-coated substratum enhances the attachment and spreading of fibroblasts.[30] Thus, although fibronectin is not required for clot formation, its presence within thrombi may mediate the influx of cells and thrombus organization.

Fibronectin has a similar affinity for collagen, which is reflected in the codistribution of fibronectin and collagen in the connective tissue extracellular matrix.[31] Covalent cross-linking of fibronectin to collagen is also observed.[32] In active granulation tissue, fibronectin appears early with invading fibroblasts before the appearance of collagenous proteins.[33] Type III collagen is formed subsequently, and when the collagen organizes into bundles, the fibronectin content is greatly reduced.

Repair of myocardium after infarction may depend, in part, on the cell translocation and tissue organizing properties of fibronectin. Pathologic stages of infarct healing include early exudation of leukocytes with dense infiltration of the damaged myocardial segment, removal of necrotic muscle fibers, and later scar formation with fibroblast activity and progressive maturation of collagen bundles. The cellular and molecular interactions of fibronectin observed in vitro are applicable to these processes of tissue repair.

Conclusions

The ubiquity of fibronectin as a major extracellular and cell surface glycoprotein has inspired investigators in various biological disciplines to study the physiologic and pathophysiologic features of this macromolecule. Our understanding of fibronectin is at an early stage, yet permits these several correlations with cardiovascular structure and function. Fibronectin can generally be regarded as a mediator of cellular contact and behavior, and perhaps its panoply of actions may ultimately be clinically important for patients with cardiovascular disorders. Disturbance of fibronectin distribution or metabolism has not been demonstrated as a primary cause of disease states. The complete in vivo role of fibronectin in the cardiovascular system awaits further exploration.

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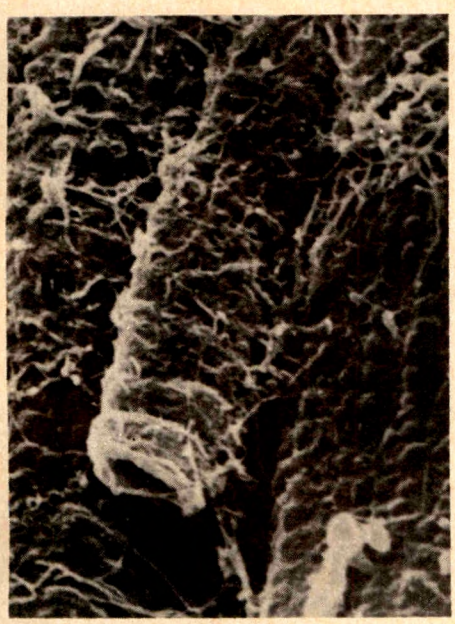
Volume 14/Number 1
Cardiovascular Clinics



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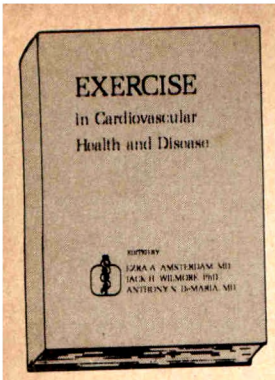

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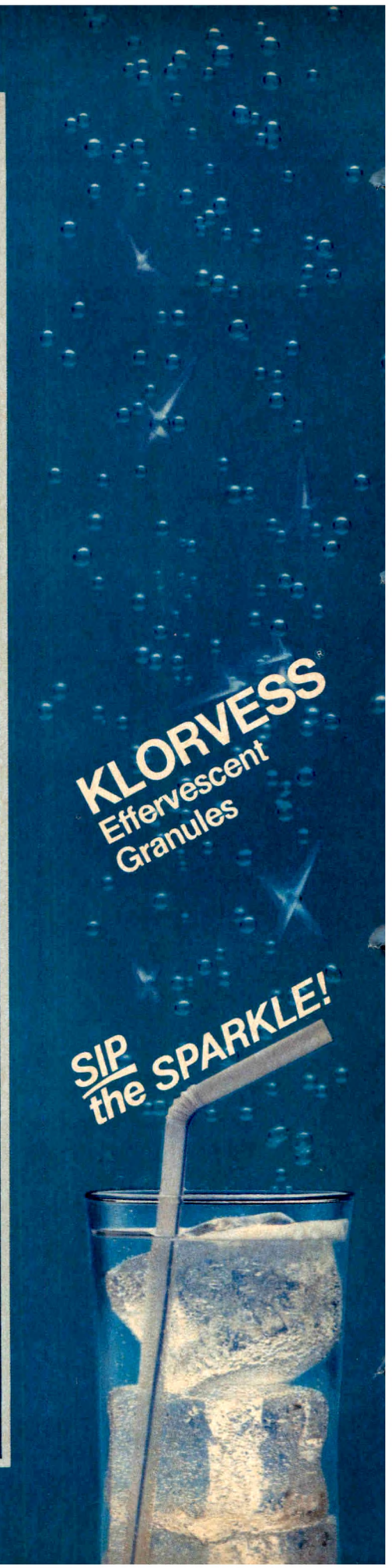

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Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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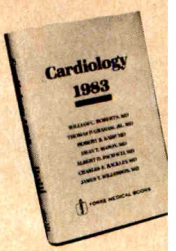

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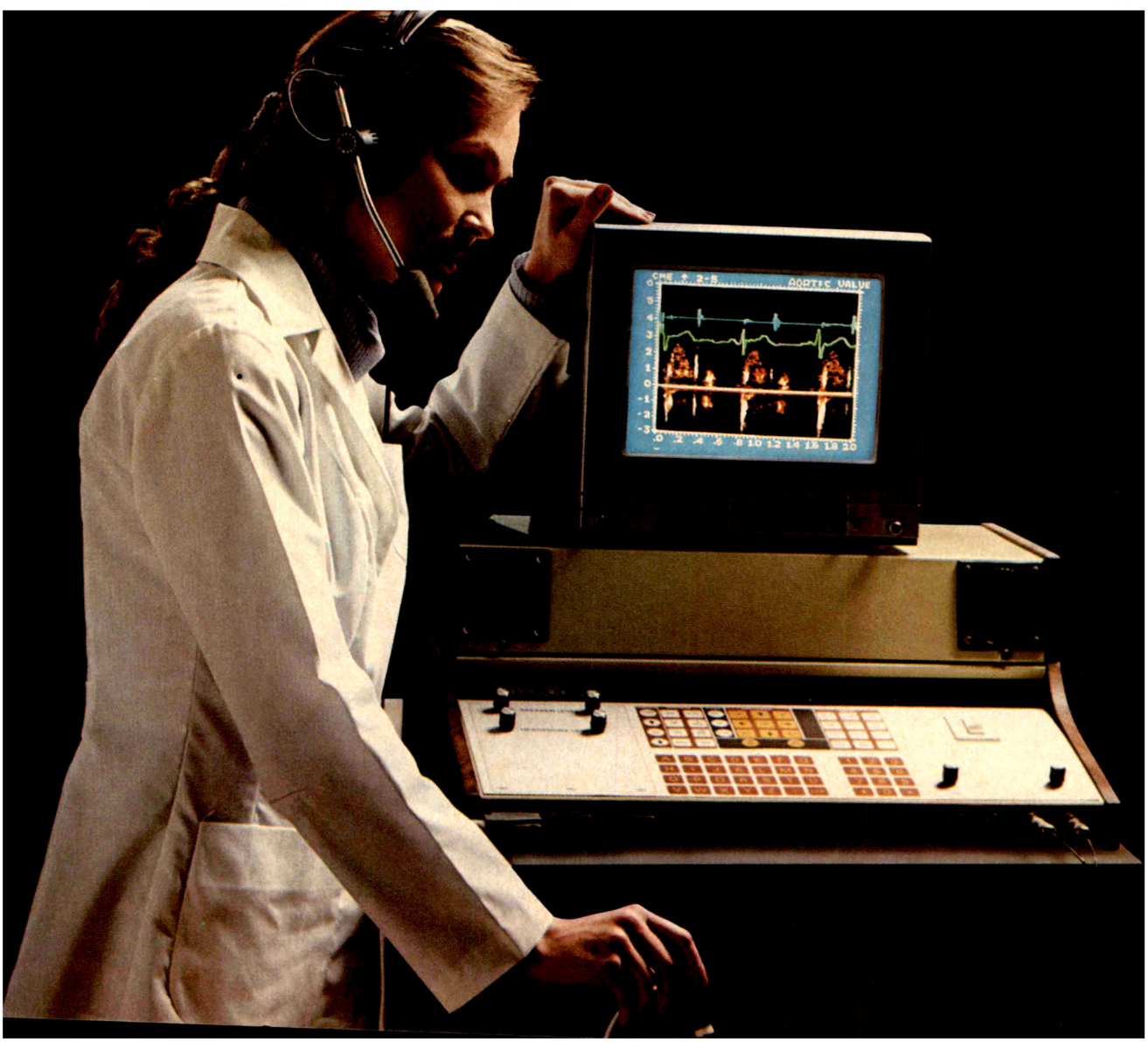
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Note: Orthostatic hypotension may indicate nitroglycerin overdosage; reduce dosage if symptoms occur. Nitrates are contraindicated in patients with increased intraocular pressure. Withdrawal should be gradual if treatment is terminated. Do not apply to distal parts of the arms and legs.

*Black CD: Transdermal drug delivery systems. *US Pharmacist* 1982 (Nov);7(11):49-78.

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DESCRIPTION
Transderm-Nitro (nitroglycerin) transdermal therapeutic system is a flat unit designed to provide controlled release of nitroglycerin through a semi-permeable membrane continuously for 24 hours following application to intact skin. Nitroglycerin (glyceryl trinitrate) is a prompt-acting vasodilator for the relief and prevention of anginal attacks. Systems are rated to release *in vivo* 2.5, 5 and 10 mg nitroglycerin over 24 hours and are in sizes of 5, 10 and 20 cm^2 respectively.

One-fifth of the total nitroglycerin in the system is delivered transdermally to the patient over 24 hours; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. The rated release of drug is dependent upon the area of the system; 0.5 mg nitroglycerin is delivered *in vivo* for every cm^2 of system size.

The Transderm-Nitro system comprises four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin; 2) a drug reservoir containing nitroglycerin adsorbed on lactose, collioidal silicon dioxide, and silicone medical fluid; 3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin; and 4) a layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

ACTIONS
When the Transderm-Nitro system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation and consequent reduced cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In clinical studies transdermal absorption of nitroglycerin from a nitroglycerin system occurred in a continuous and well-controlled manner, for a minimum of 24 hours. Therapeutic effect can be anticipated 30 minutes after application of the system and to be maintained for 30 minutes after its removal.

INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.

The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.

The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.

Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

HOW SUPPLIED

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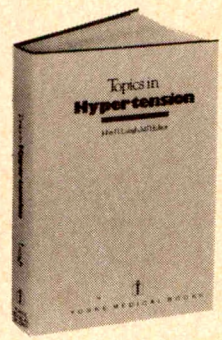

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The AJC in July 1958

CAROLE A. WARNES, MB, BS, MRCP, and WILLIAM C. ROBERTS, MD

During the past 25 years many symposia on various subjects have been published in the AJC. The first one was on mitral regurgitation (MR) and it appeared in the July, August, and September 1958 issues. Of the 9 articles included in this symposium, 3 appeared in the July issue and each will be discussed briefly herein.

Mitral Insufficiency: Historical and Clinical Aspects (Joseph B. Vander Veer)

This author reviews the concepts of MR which had been propagated during the previous 200 years. In the early part of the 20th century, the common view was that pure MR was exceedingly rare and probably of no clinical significance. This author considered that isolated MR was infrequent, that it was usually associated with mitral stenosis (MS) and, therefore, was of rheumatic origin. Because MR was the consequence of either rheumatic heart disease or infective endocarditis, its frequency might be expected to diminish even further with time because of the decreasing frequency of rheumatic fever and the increasing use of antibiotics. Of course, neither this author nor the others in this symposium were aware of the concepts of mitral valve prolapse or papillary muscle dysfunction—entities not described until 1963.

Clinical and Hemodynamic Observations in Pure Mitral Insufficiency (John Ross, Jr., Eugene Braunwald, and Andrew G. Morrow)

This is a classic study in many ways. Although it was considered infrequent, pure MR was described in 23 patients. This article is the first to focus on hemodynamic data in patients with "pure" MR. All 23 patients had left atrial pressures recorded (by transbronchial technique), 14 had left ventricular and mean pulmonary capillary wedge pressures recorded, and 7 had pulmonary capillary V wave pressures recorded.

Although this article is the first to describe left-sided cardiac pressures in a relatively large group of patients with "pure" MR, the absence of left ventricular pressures in 9 of the 23 patients prevents exclusion of associated MS in them. Thus, only 14 of the 23 may be considered to have had pure MR. Additionally, left ventricular angiography was not available at the time, and the effect of inspiration on the precordial systolic blowing murmur was not commented upon. The authors found that analysis of the left atrial pressure tracing was of considerably greater diagnostic value than analysis of the pulmonary capillary wedge pressure tracing, an interesting observation in view of the present-day use of the pulmonary wedge recording and the rare acquisition of left atrial pressures. This article disclosed a wide range of pressures in the left atrium, particularly of the V wave, and the explanation for this wide variation did not come until the concept of *acute* and *chronic* MR were presented several years later by some of the same authors.[1,2]

Hemodynamic Methods for Differentiation of Mitral Stenosis and Regurgitation (Hiram W. Marshall, Edward Woodward Jr., and Earl H. Wood)

In 1958, commissurotomy (or valvotomy) was available for patients with MS associated with little or no MR, but no proven operation was available for patients with pure or predominant MR. Thus, differentiation of patients with predominant or pure MR from those with pure or predominant MS was crucial in 1958. In this 36-page article, Marshall and associates discussed the hemodynamic features of these 2 lesions. They concluded that differentiation of predominant MR from predominant MS was not possible by analysis of left atrial, left ventricular, and pulmonary capillary wedge pressure tracings, but that the additional use of indicator dilution techniques improved diagnostic accuracy.

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Delayed Thrombolysis of Streptokinase-Resistant Occlusive Thrombus: Documentation by Pre- and Postmortem Coronary Angiography

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Marvin A. Konstam, MD
Roberta V. Fortin, BS
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Limited angiographic data and even fewer necropsy follow-up data are available regarding the fate of streptokinase-resistant intracoronary thrombus. In the patient described herein, premortem coronary angiography disclosed occlusive intracoronary thrombus, resistant to intracoronary streptokinase. Postmortem angiography performed 12 hours after completion of attempted thrombolysis demonstrated patency of the same vessel. The findings in this patient emphasize the variable behavior of occlusive thrombus after intracoronary administration of thrombolytic agents.

A 66-year-old woman was transferred to the New England Medical Center 3 hours after the onset of chest pain associated with electrocardiographic evidence of acute myocardial infarction (AMI) (Fig. 1). Coronary angiography was begun at 11:15 P.M., 4 hours and 15 minutes after the onset of AMI. The left anterior descending (LAD) coronary artery was 100% occluded immediately distal to the first septal perforator (Fig. 2a); a convex filling defect suggested that total occlusion was due to intracoronary thrombus. At 11:35 P.M., 4.5 hours after the onset of AMI, 20,000 IU of streptokinase followed by 4,000 IU/min for a total dose of 380,000 IU of streptokinase was selectively infused through the left main coronary ostium. Repeat left coronary angiography performed every 10 to 20 minutes and on completion of the infusion demonstrated persistence of the initial angiographic picture of a totally occluded LAD. The patient was transferred to the coronary care unit in stable condition. At 5:22 A.M., approximately 8.5 hours after the onset of clinical signs of AMI and 4.5 hours after completion of intracoronary streptokinase, the patient suddenly developed electromechanical dissociation and died 90 minutes later after unsuccessful cardiopulmonary resuscitation.

Postmortem examination was begun 5 hours after death. Before fixation, a barium-sulfate mixture was selectively injected into the coronary ostia at a mean pressure of approximately 80 mm Hg. Postmortem radiographs showed that the distal LAD was patent, although the proximal LAD remained focally narrowed by 90% (Fig. 2b). A histologic section taken through this site disclosed residual nonocclusive thrombus superimposed on underlying atherosclerotic plaque (Fig. 2c).

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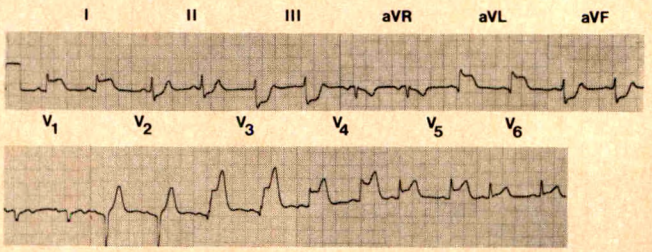

FIGURE 1. Electrocardiogram recorded shortly after admission to the emergency room demonstrates S-T segment elevation in leads I, aVL, and V_2–V_6 associated with S-T segment depression in leads II, III, and aVF; QS complexes are present in leads V_1–V_3.

Examination of the anterior left ventricular free wall of the heart revealed that it was ruptured at the site of a transmural AMI.

In 6 to 23% of patients, totally occlusive intracoronary thrombus has been reported to persist despite the administration of streptokinase after AMI.[1–4] Serial angiographic studies of such patients have been limited. Of 20 patients with total occlusion studied by Rentrop et al,[2] intracoronary thrombolysis could not be achieved in 3; repeat angiography performed 3 weeks later showed persistence of total occlusion in 1 patient, with patency of the "involved" vessel in 2. Mathey et al[3] recanalized 30 of 41 vessels totally occluded because of intracoronary thrombus; of the 11 patients in whom attempted thrombolysis was unsuccessful, 4 were restudied 7 to 21 days after AMI, and all 4 were persistently occluded. Schwarz et al[4] reported follow-up angiographic findings 4 weeks after AMI in 7 of 39 patients in whom thrombolysis was not achieved: 6 of 7 demonstrated persistent occlusion of the "involved" vessel.

Necropsy studies of patients with totally occlusive thrombus resistant to streptokinase have, to our knowledge, been limited to a single patient.[3] In this 71-year-old patient, 2 hours of intracoronary streptokinase infusion failed to reopen a totally occluded right coronary artery; necropsy performed 2 days later demonstrated persistent occlusion due to thrombus superimposed on an atherosclerotic stenosis.

The present case is unusual in that it represents 1 of the few instances in which total occlusion documented by premortem coronary angiography was evaluated by postmortem coronary angiography performed <12 hours later. Postmortem angiography documented delayed thrombolysis of an apparent streptokinase-"resistant" total occlusion during the relatively brief interval of time separating the 2 angiographic studies.

The dynamic behavior of intracoronary thrombus resistant to streptokinase illustrated in this patient has important methodologic implications for investigations designed to evaluate the role of thrombus and thrombolysis in AMI. First, failure to achieve thrombolysis acutely does not mean that thrombolysis will not ultimately occur; indeed, as demonstrated in the present

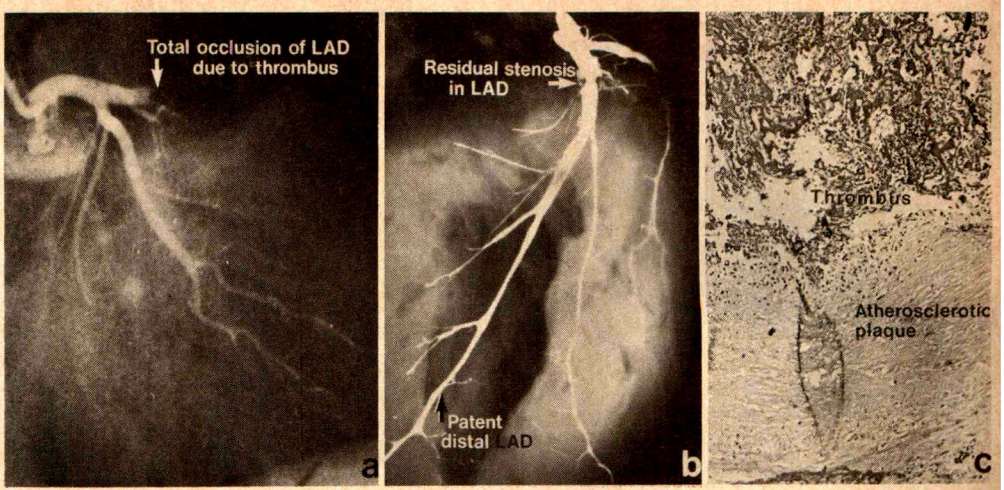

FIGURE 2. a, premortem arteriogram recorded before intracoronary infusion of streptokinase demonstrates a 100% occlusion of the left anterior descending coronary artery (LAD) immediately after the take-off of the first septal perforator. **b,** postmortem coronary arteriogram demonstrates a patent LAD with a residual proximal focal stenosis resulting in a 90% diameter narrowing. **c,** histologic section taken through the site of residual stenosis demonstrated by postmortem angiography shows a nonocclusive thrombus superimposed on underlying atherosclerotic plaque. (Hematoxylin and eosin; magnification ×20, reduced 41%.)

case, thrombolysis may occur very shortly after completion of the angiographic study. Thus, if a patient underwent thrombolysis <3 hours after the onset of AMI and the infusion were arbitrarily discontinued after 1 hour because of lack of recanalization, thrombolysis could still occur in <6 hours, a time window that might be expected to confer therapeutic benefit. Second, serial observations in the present case confirm the suggestion of DeWood et al[5] that spontaneous thrombolysis is the most likely explanation for their finding that the incidence of intracoronary thrombus decreased with increasing time after infarction. Furthermore, DeWood's patients classified as "false-positive" because the preoperative angiographic diagnosis of intracoronary thrombus was followed by failure to retrieve thrombus at the time of surgery may, in fact, have represented patients with spontaneous thrombolysis rather than a false-positive angiographic diagnosis. Third, absence of occlusive intracoronary thrombus at necropsy after AMI cannot necessarily be interpreted as evidence that no intracoronary occlusion existed during life; in fact, spontaneous thrombolysis, as demonstrated in this patient, may explain variations in the prevalence of occlusive thrombus noted in patients with AMI studied either at necropsy[6] or at angiography.

Acknowledgment: We thank Drs. Harvey Zarren, Jerry Perlow, and Daniel Wistran of Lynn, Masachusetts, who referred this patient to our catheterization laboratory.

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Pulsus Alternans After Valve Replacement for Aortic Regurgitation

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Pulsus alternans is characterized by regular alternation of strong and weak pulses. It occurs most commonly in patients with severe left ventricular (LV) dysfunction.[1,2] Herein, we describe pulsus alternans during pacing-induced tachycardia in 2 patients after aortic valve replacement (AVR) for severe aortic regurgitation (AR).

The 2 patients were among a larger group of patients studied to evaluate LV pressure-volume relation with pacing. Both patients had isolated severe AR seen by cardiac catheterization. Both were men, aged 26 and 62 years.

The technique for combined hemodynamic and radionuclide evaluation from this laboratory has been previously described.[3] In brief, the thermodilution cardiac output, pulmonary arterial wedge pressure, and pulmonary arterial pressure were measured by a triple lumen Swan-Ganz catheter. The systemic pressure was measured by an indwelling catheter in the femoral artery. The LV ejection fraction and volume were measured by first-pass radionuclide ventriculography with a multicrystal gamma camera. Pacing was performed with a catheter in the coronary sinus and terminated in the 2 patients because of development of

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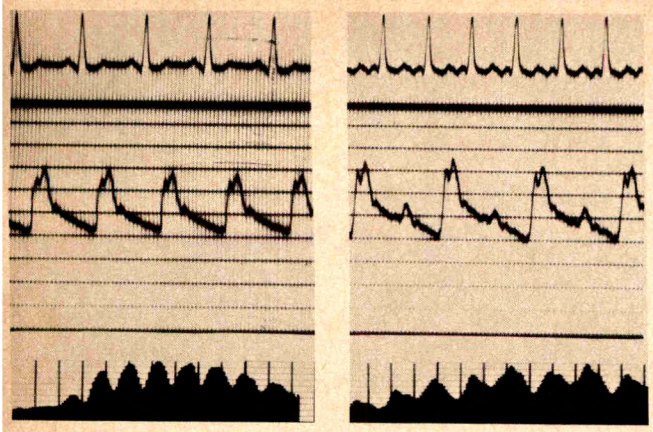

FIGURE 1. Femoral artery pressure tracings (scale 0 to 200 mm Hg) and time-activity curves in the control state (**left**) and with rapid pacing in the postoperative study in Patient 1 (**right**). The time-activity curve was obtained from the left ventricular region of interest using first-pass radionuclide ventriculography. The peaks represent end-diastoles and the troughs represent end-systoles. The difference between peaks and troughs represents the stroke volume counts in individual beats. The time-activity curve in the control state is normal, showing a gradual increase followed by a decrease in end-diastolic counts in sequential cardiac cycles as the bolus of radioactivity enters and leaves the ventricle. With pacing (pacing spikes are noted on the electrocardiogram), there is pulsus alternans and alternans of the end-diastolic and stroke volume counts. The time-activity curve was not obtained simultaneously with the pressure tracing.

TABLE I Pertinent Data in the 2 Patients Before Aortic Valve Replacement

	Patient 1		Patient 2	
	Control	Pacing	Control	Pacing
HR (beats/min)	78	150	72	140
CI-TD (liters/min/m^2)	3.2	3.7	3.4	3.6
PCW (mm Hg)	14	14	24	18
PAP (mm Hg)	18	18	30	25
FAP (mm Hg)	100	100	90	100
EDVI (ml/m^2)	261	156	330	156
ESVI (ml/m^2)	109	101	208	106
EF (%)	41	35	37	32
RF (%)	72	38	61	49

CI-TD = cardiac index by thermodilution; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; FAP = mean femoral arterial pressure; HR = heart rate; PAP = mean pulmonary arterial pressure; PCW = mean pulmonary capillary wedge pressure; RF = regurgitant fraction.

TABLE II Pertinent Data in the 2 Patients After Aortic Valve Replacement

	Patient 1		Patient 2	
	Control	Pacing	Control	Pacing
HR (beats/min)	96	140	80	140
CI-TD (liters/min/m^2)	3.9	3.6	3.4	3.2
PCW (mm Hg)	8	9	19	22
PAP (mm Hg)	13	14	24	30
FAP (mm Hg)	100	100	98	96
EDVI (ml/m^2)	87	55	137	77
ESVI (ml/m^2)	46	29	94	53
EF (%)	47	47	31	31

CI-TD = cardiac index by thermodilution; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; FAP = mean femoral arterial pressure; HR = heart rate; PAP = mean pulmonary arterial pressure; PCW = mean pulmonary capillary wedge pressure.

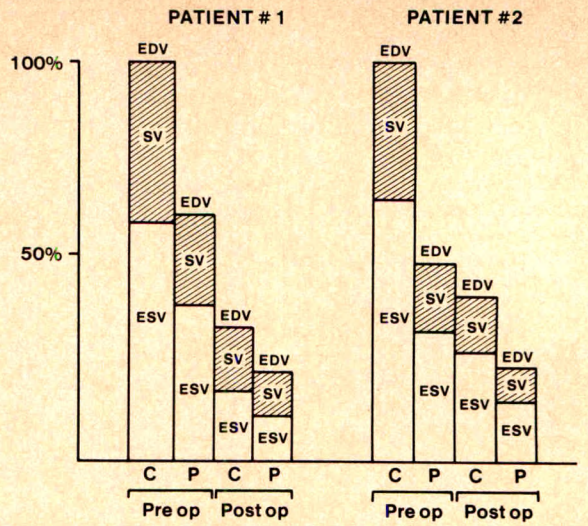

FIGURE 2. Changes in left ventricular volumes with pacing before and after valve replacement. C = control; EDV = end-diastolic volume; ESV = end-systolic volume; P = pacing; Postop = postoperative; Preop = preoperative; SV = stroke volume.

Wenckebach-type atrioventricular block. The control and pacing studies were done 7 to 10 days before and after uneventful AVR.

The pertinent data before replacement are shown in Table I, and after replacement in Table II. Pulsus alternans was not observed with pacing before AVR, but was present in both patients afterwards. The time-activity curves from the LV region also are shown in Figure 1. There is alternation in stroke volume counts with pacing. AVR resulted in a decrease in end-diastolic volume. Since pacing resulted in a decrease in end-diastolic volume before and after AVR, the pacing end-diastolic volume was considerably smaller after than before surgery. AVR resulted in a 67% decrease in end-diastolic volume in the first patient, and a 58% decrease in the second patient. After AVR, pacing resulted in a 79% decrease in end-diastolic volume in the first patient and a 77% decrease in the second compared with preoperative control measurements (Fig. 2). The ejection fraction with pacing was higher in the first patient and unchanged in the second after AVR.

Several mechanisms may contribute to pulsus alternans: alternation in ventricular end-diastolic volume (the Starling mechanism), alternation in contractile force without end-diastolic volume change (the "myocardial" theory), or a combination of both mechanisms.[1,4] Alternation in cardiac cycle length and time available for ventricular filling or relaxation may further influence these basic determining factors. Persistent alternans is associated with relatively severe LV dysfunction and appears to occur mainly on the basis of the myocardial mechanism.[1] In aortic stenosis, alternation of the arterial pulse is smaller than the ventricular alternation, due to the attenuating effect of the valvular obstruction.

Our report suggests that marked reduction in LV end-diastolic volume, induced by atrial pacing after AVR for AR, can precipitate pulsus alternans (Fig. 2). The alternation in end-diastolic volume (Fig. 1) indicates that pulsus alternans occurred on the basis of the

Starling mechanism. It is possible that pulsus alternans, by the same mechanism, may be encountered during sinus tachycardia in the early postoperative period after AVR.

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Contrast Echocardiography to Reduce Ionizing Radiation Associated With Cardiac Catheterization During Pregnancy

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The use of radiation for diagnostic imaging should be minimized during pregnancy because of hazards to the fetus.[1,2] Cardiac catheterization, however, is sometimes indicated for diagnostic, therapeutic, and prognostic reasons. This report describes the use of two-dimensional (2-D) contrast echocardiography as a substitute for cineangiography in the assessment of cardiac valvular function in pregnancy.

A 23-year-old woman in her 31st week of pregnancy was admitted for dyspnea and palpitations, which started at her 20th gestational week and worsened progressively thereafter. On arrival in the emergency room the respiratory rate was 28 breaths/min, pulse 150 beats/min, and blood pressure 112/76 mm Hg. Examination suggested mitral stenosis and regurgitation (MR), aortic regurgitation, and possible aortic stenosis. The electrocardiogram showed atrial flutter with an atrial rate of 300 beats/min and 2:1 atrioventricular conduction. Right-sided cardiac catheterization was done using a Swan-Ganz catheter under pressure monitoring only without the use of fluoroscopy. A 7Fr pigtail catheter was then placed in the left ventricle with the aid of fluoroscopy. Hemodynamic measurements revealed 17 mm Hg pressure gradient across the mitral valve, but no aortic stenosis. While 2-D echocardiography was performed in multiple views, 10 ml repeated injections of 5% dextrose in water was injected into the left ventricle after vigorous agitation and removal of any visible bubbles. The injection into the left ventricle was immediately followed by complete opacification of the entire left atrium (Fig. 1). The contrast density was less than that in the ventricle, suggesting moderately severe MR. The catheter was then pulled back under pressure monitoring into the aortic root. The tip of the catheter was positioned with the aid of fluoroscopy 1 loop diameter above the aortic valve. The injection into the aortic root was followed by the appearance of microbubbles in the left ventricle that did not completely fill the chamber, suggesting moderate aortic regurgitation. The presence of microbubbles in the left atrium after the aortic root injection was further evidence of the presence and severity of MR (Fig. 2). Because of the inability to precisely assess left ventricular volume and, therefore, the diastolic blood flow across the mitral valve, we could not calculate the mitral valve area. To control the rapid heart rate, propranolol was added to the patient's medical regimen. Because of significant risks of double valve replacement and the already advanced stage of pregnancy, a trial of medical therapy with arteriolar dilators seemed appropriate. The patient was, therefore, started on hydralazine. Her condition improved and she was discharged home on the ninth hospital day. One week after discharge she was readmitted for premature rupture of membranes, and 18 hours later, in her 33rd gestational week, the patient delivered a normal infant whose size was adequate for

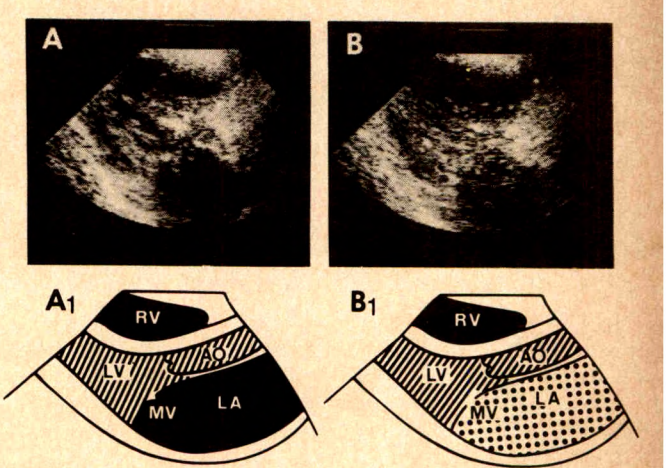

FIGURE 1. Two-dimensional echocardiogram in the parasternal long-axis view before (**A**) and during an injection of dextrose in water into the left ventricle (**LV**) (**B**). Multiple microbubbles occupy the entire cavity of the left atrium (LA) because of significant mitral regurgitation (**large dots in B_1**). **Diagonal lines** in A_1 and B_1 reflect echo artifacts in the aorta (AO) and left ventricle.

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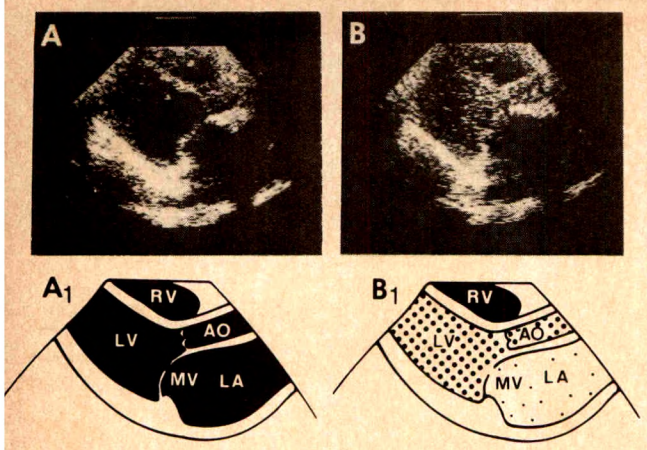

FIGURE 2. A still frame of a 2-D echocardiogram in a modified parasternal long-axis view showing the left ventricle (LV), left atrium (LA), right ventricle (RV), aorta (AO), mitral valve (MV), and aortic valve before (**A**) and during (**B**) an injection of dextrose in water into the aortic root. A_1 and B_1 are diagrams of **A** and **B**. Notice the opacification of the entire left ventricular cavity (**large dots in B_1**) with some microbubbles seen in the left atrium (**small dots in B_1**). Other abbreviations as in Figure 1.

gestational age. The course of labor, delivery, and the postpartum period were uneventful.

The significantly increased burden on the cardiovascular system during pregnancy may result in a rapid deterioration of maternal heart disease to a potentially lethal condition. Cardiac catheterization, therefore, is sometimes indicated during pregnancy, especially in patients in whom cardiac surgery is being considered.

Radiologic examination during pregnancy is associated with potential biological risk to the embryo or fetus.[1,2] The risks include resorption or death to the embryo, congential malformations, cancer induction, and genetic changes. The adverse effect of radiation varies with the developmental stage of the fetus, and the likelihood of side effects is linearly proportional to the dose of absorbed radiation.[1] The present study demonstrates the use of contrast echocardiography during cardiac catheterization to collect diagnostic information usually obtained by fluoroscopy or cineangiography, and thus to significantly reduce exposure to x-ray radiation.

Our case supports a previous report by Meltzer et al,[3] who performed cardiac catheterization in a pregnant woman under 2-D echocardiographic control without the use of x-ray radiation. Unlike their experience, however, we could not achieve adequate echocardiographic visualization of the cardiac catheter in the aortic root in our patient. As placement of the cardiac catheter under echocardiographic technique alone in the aortic root and left ventricle is not always possible and is potentially unsafe,[4] the use of x-ray radiation is not completely avoidable. However, utilization of contrast echocardiography can minimize the use of ionizing radiation and, in combination with the hemodynamic data, can provide a reliable assessment of valvular disease. This technique may be used effectively, therefore, in patients with valvular heart disease who are undergoing cardiac catheterization during pregnancy.

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Prolonged Survival (62 Years) With Single Ventricle

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Although single ventricle usually results in death in infancy or childhood, additional obstruction to pulmonary blood flow can permit prolonged, often asymptomatic survival.[1–5] The oldest patient described with single ventricle that we are aware of was 41 years of age at death.[6] We recently studied a man who lived 62 years with a single ventricle.

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A precordial murmur was heard at birth. At age 26 years episodic palpitations and fatigue were noted. Cardiac catheterization at age 44 demonstrated an "inoperable hole in the heart" (records not available). The patient continued to experience minimal symptoms until age 62, when dyspnea on exertion appeared. Three months later, when he was in New York Heart Association functional class III from dyspnea and fatigue, cardiac catheterization was performed.

The systemic ventricle was entered from the right atrium. There was no systolic gradient across the aortic outflow tract, but a 130 mm peak-to-peak systolic gradient was present across the infundibulum. Pulmonary arterial pressures were normal. Oximetry demonstrated oxygen saturation in the left ventricle of 83% and femoral artery saturation of 93%. Cut film angiography demonstrated a single large ventricle that was a morphologic left ventricle. The pulmonary artery originated from this ventricle, and subpulmonic stenosis was present. The pulmonary trunk was slightly dilated. There was anterograde flow from the morphologic left ventricle through a bulboventricular foramen into a hypoplastic right ventricle which lay superior and to the left of the left ventricle. The L-transposed aorta originated from the right ventricle. The aortic valve was superior, anterior, and to the left of the pulmonary trunk.

Two months after catheterization second-degree heart block was noted, for which a transvenous pacemaker was

placed. Six months after catheterization he had sudden cardiac arrest despite electrocardiographic evidence of continued pacemaker function. Autopsy was not obtained.

The clinical course of patients with single ventricle is in large part determined by the extent of pulmonic or subpulmonic stenosis. If there is no obstruction to pulmonic flow, congestive heart failure ensues early. With excessive pulmonic stenosis, hypoxia and cyanosis results. However, as this case clearly demonstrates, the "optimal" degree of obstruction of pulmonary blood flow can result in physiologic palliation with prolonged survival.

Our patient provides an excellent example of a hemodynamic phenomenon described by Rahmitoola et al,[6] who noted that L-transposition of the great vessels usually provides preferential streaming of oxygenated blood from the left atrium into the systemic circulation. Thus, our patient had a systemic oxygen saturation of 93%, which was higher than the saturation in the left ventricle. He had neither cyanosis nor polycythemia. The cause of death in our patient is uncertain.

Acknowledgment: We would like to thank Drs. Charles Steinberg and Kalman Berenyi for allowing us to report on their patient, and for follow-up information.

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Histiocytoid Cardiomyopathy: A Cause of Sudden Death in Apparently Healthy Infants

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Victor J. Ferrans, MD, PhD
E. Rene Rodriguez, MD
F. Robert Lewis, MD
William C. Roberts, MD

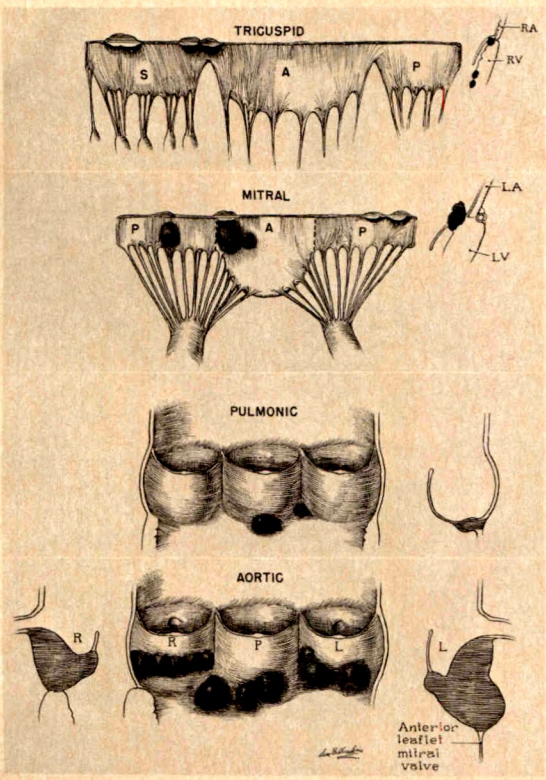

FIGURE 1. Drawing illustrating the distribution of the discrete nodules on the 4 cardiac valves and adjacent myocardial walls. A = anterior leaflet; L = left coronary cusp of aortic valve; LA = left atrium; LV = left ventricle; P = posterior leaflet; R = right coronary cusp of aortic valve; RA = right atrium; RV = right ventricle; S = septal leaflet of tricuspid valve.

Although common in adults, sudden unexpected cardiac death in apparently healthy infants is unusual. Herein we describe a child who died suddenly from infantile cardiomyopathy with histiocytoid myocytes, a poorly understood but clinically and morphologically distinct entity.

A previously healthy-appearing and normally developed 19-month-old white girl was noted to have slight fever (39°C) by her parents and she was given 80 mg of aspirin. Six hours later she awakened, the body temperature was obviously elevated, she quivered with apparent chills and suddenly stopped breathing. At necropsy, the heart weighed 60 g (expected normal weight ≤54 g). Numerous discrete smooth nodules and flat patches of soft yellow-tan tissue were present on all 4 cardiac valves, papillary muscles, and mural endocardial surfaces of both ventricles (Fig. 1 and 2). His-

FIGURE 2. Photograph illustrating a nodule on the atrial aspect of the anterior mitral leaflet.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received and accepted April 12, 1983.

* On leave of absence from the Department of Pathology, Washington University, St. Louis, Missouri.

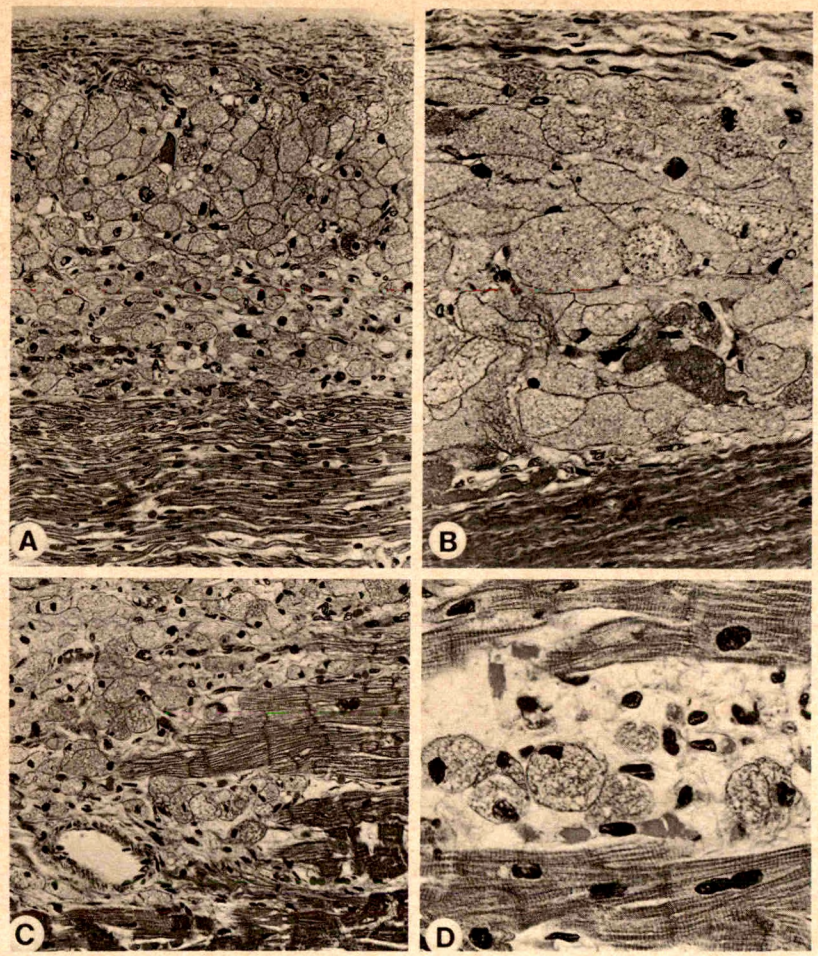

FIGURE 3. Histology of the histiocytoid cells in the patient described. (1-μm–thick plastic sections [glycolmethacrylate embedding] hematoxylin-eosin stain). **A,** section of portion of left ventricular papillary muscle showing a nodule to be composed of numerous histiocytoid cells with large, bizarre nuclei with vacuolated cytoplasm. Myofibrils are not present in these cells, in contrast to subjacent normal myocytes (**bottom**) (× 250, reduced 40%). **B,** higher magnification view of histiocytoid cells (×700, reduced 40%). **C,** transitional zone, showing hypertrophied myocytes adjacent to the histiocytoid cells. Other myocytes (**lower right**) show contraction band necrosis (×250, reduced 40%). **D,** isolated histiocytoid cells located in loose connective tissue between 2 layers of myocytes (×1,000, reduced 40%).

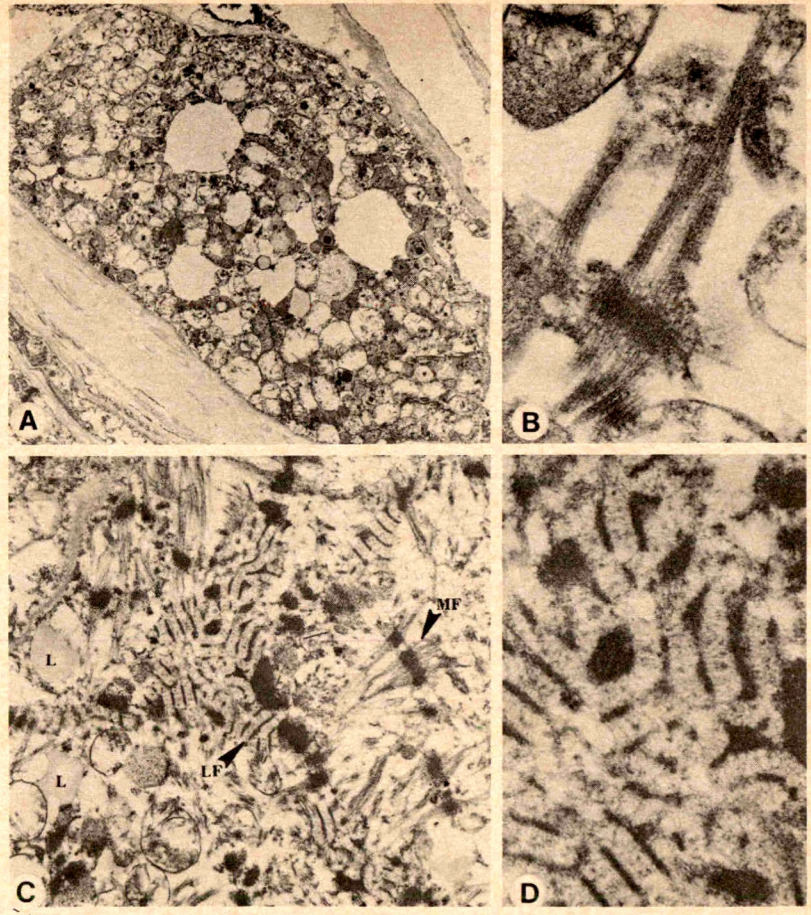

FIGURE 4. Ultrastructure of histiocytoid cells. (Ultrathin sections stained with uranyl acetate and lead citrate.) **A,** low magnification view of isolated histiocytoid cells. The cell lacks contractile elements and contains numerous mitochondria and a few large, clear vacuoles. Many mitochondria are swollen and damaged; others have densely packed cristae. Most mitochondria contain dense inclusions, probably the result of postmortem autolysis (×4,700, reduced 40%). **B,** high magnification view of part of histiocytoid cell, showing remnants of myofibrils, clearly identified by the presence of thick and thin myofilaments and Z band material (×36,000, reduced 40%). **C,** histiocytoid cell contains partially lysed myofibrils (MF), a large cluster of leptofibrils (LF), and several lipid droplets (L) (×18,000, reduced 40%). **D,** higher magnification view of leptofibrils shown in the center of Figure 3C. These structures are composed of periodic bands, with a spacing of 2,000 angstroms (A), of electron-dense material interconnected by filaments of about 50 A in diameter. The function of these structures is unknown (×37,000, reduced 40%).

tologic and ultrastructural examination of the nodules and adjacent myocardium disclosed distinctive histiocytoid cells (Fig. 3) containing abundant mitochondria, occasional lipid droplets, leptofibrils, and fragments of myofibrillar material (Fig. 4).

At least 20 necropsy patients with fatal histiocytoid cardiomyopathy in infancy have been reported.[1,2] In almost all these cases, a seemingly healthy child (aged 2 to 24 months; 90% female) died suddenly, documented in some to be the result of either a supraventricular or a ventricular arrhythmia. All had histiocytoid degeneration of myocardial cells at necropsy. Several patients had developed mild febrile illnesses before death. It appears that the clinical manifestations are due to a cardiomyopathic process leading to myocellular degeneration and transformation of myocytes into cells resembling histiocytes. The presence of leptofibrils in histiocytoid myocytes, first reported by Silver et al,[2] is of unknown significance. The degenerative process must antedate the development of arrhythmia, which occurs late. The cause of the cardiomyopathy is obscure.

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Amiodarone Distribution in Human Tissues After Sudden Death During Holter Recording

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Alberto Volpi, MD
Vincenzo D'Aranno
Gianni Tognoni, MD
Paolo Giani, MD

Death of a Holter-monitored patient enrolled in a controlled evaluation of the antiarrhythmic efficacy of amiodarone is of specific interest on account of the concomitant information it provides on blood and tissue drug levels.

A 60-year-old man was admitted to the hospital for investigation of recurrent episodes of palpitation. Previously, he had a nontransmural inferior myocardial infarction that healed. Thereafter, he had rare episodes of angina pectoris. Blood pressure was 135/80 mm Hg. Precardial endings were normal. Resting electrocardiogram showed a small Q wave in leads II, III, and aVF, a normal repolarization phase, and monomorphous ventricular extrasystoles. He entered a controlled trial where the efficacy of amiodarone, 400 mg and 200 mg, was tested in successive periods of 28 days, according to the scheme presented in Table I, which also reports the results of amiodarone blood levels and of thyroid hormone determinations taken at the intervals planned in the protocol. The patient was treated with nifedipine (40 mg/day) for stable effort angina. The patient died suddenly after ventricular fibrillation at the time of the scheduled hospital control, 20 minutes after starting the 24-hour Holter monitoring. At necropsy, parts of organs were sampled, and analyzed by the standard method used in our laboratory.[1] The amiodarone concentration in various tissues and ratios of tissue concentration to steady state blood levels (0.94 μg/ml) are reported in Figure 1.

From the Laboratory of Clinical Pharmacology, Mario Negri Institute, Milan, Italy. Manuscript received December 9, 1982; revised manuscript received April 11, 1983, accepted April 12, 1983.

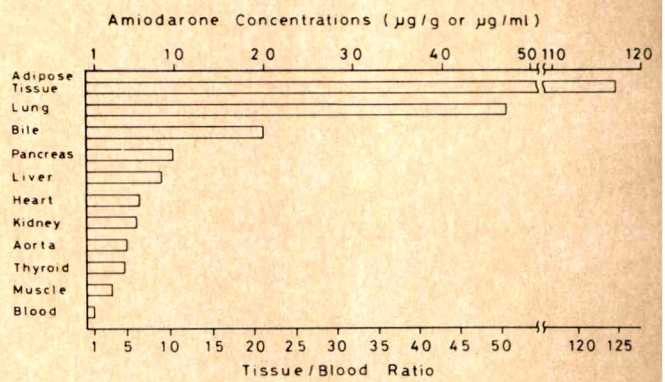

FIGURE 1. Amiodarone distribution in various tissues.

TABLE I Study Protocol and Biochemical Profile

	Day 0	Day 28	Day 56
	↑ Baselines Values	Amiodarone 400 mg/day ↑ 1st Control	Amiodarone 200 mg/day ↑ 2nd Control
Thyroid hormones			
Total thyroxine (TT_4) (nmol/liter)	120	136	130
Free thyroxine (FT_4) (pmol/liter)	11.2	12.7	13.8
Total triiodothyronine (TT_3) (nmol/liter)	2.1	2.0	3.2
Free triiodothyronine (FT_3) (pmol/liter)	6.2	5.3	10.1
Thyroid-stimulating hormone (TSH) (μmol/ml)	2.2	1.2	0.6
Blood amiodarone level (μg/ml)	0	0.95	0.94

The case described here represents the first amiodarone-treated patient for whom a fully documented report is available at the occurrence of sudden death. According to the criteria of the study protocol[2,3] the patient had been classified among the responders to antiarrhythmic therapy and after the first period of the trial his subjective report did not suggest any relevant symptoms during the month before sudden death. Examination the day of death gave findings similar to the previous ones if one excludes an increase in heart rate (from 59 to 75 beats/min). The possible relation of amiodarone treatment with the thyroid status[4] suggests the importance of close monitoring of thyroid function. No clear inference could be drawn from absolute drug concentrations or their ratios. The 2 different regimens of amiodarone (400 and 200 mg) in the 2 study periods did not seem to modify blood drug concentrations, which, however, were not correlated to drug efficacy. The pattern of distribution of amiodarone in various organs confirms the expected preferential concentration in lipid-rich tissues. The very high ratio for lungs, although not associated with any clinical or objective findings, should be viewed in the light of repeated reports of relevant pulmonary side effects.[5] The relatively small amount of amiodarone found in the thyroid gland could support the hypothesis of a peripheral action of the drug.[6] Conversely, the relatively high whole heart tissue concentration reveals little about the level-efficacy relationship.

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Severe Mitral Regurgitation Immediately After Mitral Valve Replacement With a Parietal Pericardial Bovine Bioprosthesis

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Manuscript received and accepted April 5, 1983.

The occurrence of severe mitral regurgitation (MR) immediately after mitral valve replacement (MVR) is exceedingly rare. One cause is interference with closure of a prosthetic occluder by the left ventricular wall, calcific deposits, or residual unexcised mitral leaflet or chordae tendineae.[1] Another cause is incomplete obliteration by suture of the space between the prosthetic or bioprosthetic ring and the native anulus, resulting in a paraanular communication.[1] A third and hitherto unreported cause of severe MR immediately after MVR by a bioprosthesis is described in the patient below.

A 64-year-old man who had had a precordial systolic murmur for many years had been asymptomatic until 25

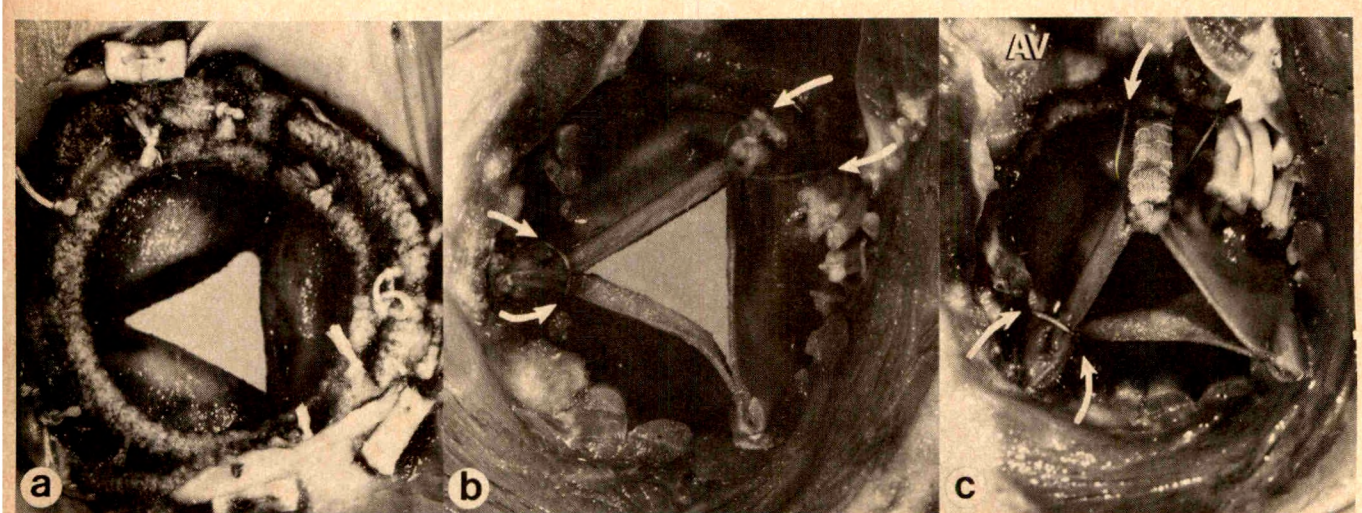

FIGURE 1. Mitral bioprosthesis in the patient described. **a,** view from left atrium showing a triangular orifice. **b and c,** 2 views from the left ventricular aspect. The **arrows** point to the 2 sutures which encircled the stents, causing tautness of the cusps and preventing them from coapting during ventricular systole.

days before MVR, when signs of active infective endocarditis appeared; severe congestive heart failure followed shortly thereafter. Group B beta hemolytic streptococcus was grown on blood cultures. A grade 3/6 precordial apical systolic blowing murmur consistent with MR was audible. The pulmonary arterial wedge mean pressure was 35, V-wave 50, and pulmonary arterial pressure 57/20 mm Hg. At MVR, a vegetation was present on the posterior mitral leaflet to which several chordae had ruptured; the leaflet appeared to prolapse toward left atrium. The purely regurgitant valve was replaced with a 25-mm Ionescu-Shiley bioprosthesis. The patient's early postoperative course was characterized by systemic hypotension and coma. A murmur consistent with MR was heard on precordial examination 2 days after operation. He died 8 days after operation, never having regained consciousness. At necropsy, the heart weighed 690 g. Sutures surrounded 2 of the 3 stents of the mitral bioprosthesis, causing a straight-line stretching of the margins of the bioprosthetic cusps between the 3 commissures. The result was a triangular-shaped severely incompetent bioprosthetic orifice (Fig. 1).

Thus, sutures encircling 2 of the 3 bioprosthetic stents tautened the cusps, producing severe MR. The left atrium should not be closed after MVR until it is clear that the cusps of a tissue valve or the occluder of a mechanical valve[2] are freely mobile.

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LETTERS*

RETRACTION OF A REPORT PUBLISHED IN THE AJC

In response to the announcement by Harvard University that John R. Darsee, MD, fabricated research data while serving as a research fellow in their School of Medicine, we initiated an extensive investigation by both internal and external committees of Dr. Darsee's work at Emory University. This letter concerns a publication in *The American Journal of Cardiology* that was authored by Dr. Darsee: "Transcutaneous Doppler method of measuring cardiac output—II. Noninvasive measurement by transcutaneous Doppler aortic blood velocity integration and M mode echocardiography," by Darsee JR, Walter PF, and Nutter DO (Am J Cardiol 1980;26:613–618).

The original Doppler records collected and analyzed by Dr. Darsee were not available for review by our investigative committees. Because we cannot validate the data that formed the basis for this article, and in view of the widespread evidence of fraudulent practice in other publications authored by Dr. Darsee, we wish to retract this report.

We apologize to the Editor-in-Chief and the *Journal* for any embarrassment and inconvenience that might result from our investigation of Dr. Darsee's research activities and publications.

James F. Glenn, MD
Dean, School of Medicine
Emory University

Donald O. Nutter, MD
Professor of Medicine (Cardiology)
School of Medicine

Paul F. Walter, MD
Associate Professor, Department of Medicine, School of Medicine

•

RETRACTION OF A REPORT PUBLISHED IN THE AJC

Harvard University and the National Institutes of Health have both completed committee reports that concluded that John R. Darsee, MD, fabricated research data while serving as a research fellow at Harvard University and performing research supported by the National Heart, Lung, and Blood Institute.

An intensive investigation has been performed by both internal and external committees of Emory University concerning Dr. Darsee's previous publications while at Emory University. This letter concerns the report "Transcutaneous method of measuring Doppler cardiac output—I. Comparison of transcutaneous and juxta-aortic Doppler velocity signals with catheter and cuff electromagnetic flowmeter measurements in closed and open chest dogs," by Darsee JR, Mikolich JR, Walter PF, and Schlant RC (Am J Cardiol 1980;46:607–612).

In our investigation we were unable to obtain and verify the original data reported in the above article. Due to our inability to verify the observations reported in this paper as well as the widespread evidence of fraudulent practice in other abstracts and reports authored by Dr. Darsee, we believe that the work described in this report should be considered of uncertain validity. We wish to retract this report.

We apologize to the *Journal* and to its readers for any embarrassment and inconvenience that might have resulted from this publication and from our investigation of Dr. Darsee's research activities and publications.

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Emory University School of Medicine

Robert C. Schlant, MD
Professor of Medicine (Cardiology)
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James F. Glenn, MD
Dean, Emory University School of Medicine
Atlanta, Georgia

RETRACTION OF 3 ABSTRACTS PUBLISHED IN THE AJC

In response to the announcement by Harvard University that John R. Darsee, MD had fabricated research data while serving as a research fellow in their School of Medicine, we initiated an extensive investigation by both internal and external committees of Dr. Darsee's work at Emory University. This letter concerns 3 abstracts authored by Dr. Darsee and published in *The American Journal of Cardiology:*

> Darsee JR, Miklozek CL, Heymsfield SB, Nutter DO. Complement-resistant lymphocytes in mitral valve prolapse. Am J Cardiol 1979;43:367.
>
> Darsee JR, Fincher RE, Fincher M, Miklozek CL, Someren AO, Hurst JW. The heart in pancreatitis: a combined clinicopathologic study of 128 cases. Am J Cardiol 1980;45:395.
>
> Darsee JR, Anton S, Miklozek CL, Someren AO. Is nonfamilial asymmetric septal hypertrophy a different histological disorder? Am J Cardiol 1980;45:492.

The Emory University School of Medicine faculty members whose names appear on these abstracts did not participate in the reported research or review the abstracts before their submission. In most cases the co-authors were not aware that the abstracts had been submitted or published. Most of these abstracts were submitted for publication or appeared in print after Dr. Darsee left Emory University (July 1979). For the aforestated reasons and in view of the widespread evidence of fradulent practice in other reports authored by Dr. Darsee, we believe that these abstracts are invalid, and in some cases it seems likely that the data were fabricated. We request that the abstracts be retracted.

We apologize to the Editor-in-Chief and the *Journal* for any embarrassment and inconvenience that might result from our investigation of Dr. Darsee's research activities and publications.

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J. Willis Hurst, MD
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RETRACTION OF A PUBLISHED ABSTRACT

Irregularities in data collected in my laboratory by a collaborator, described in *Harvard University Gazette* (February 18, 1983;78:1) and *Science* (1983;220:31–35) have brought into question the validity of the data listed in the abstract below, which was retracted as a full-length publication. Because of these circumstances, it is my opinion that this abstract should be retracted: Darsee JR, Kloner RA. The no-reflow phenomenon: not a time limiting factor for reperfusion following coronary occlusion (abstr). Am J Cardiol 1980;45:394.

Robert A. Kloner, MD, PhD
Boston, Massachusetts

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

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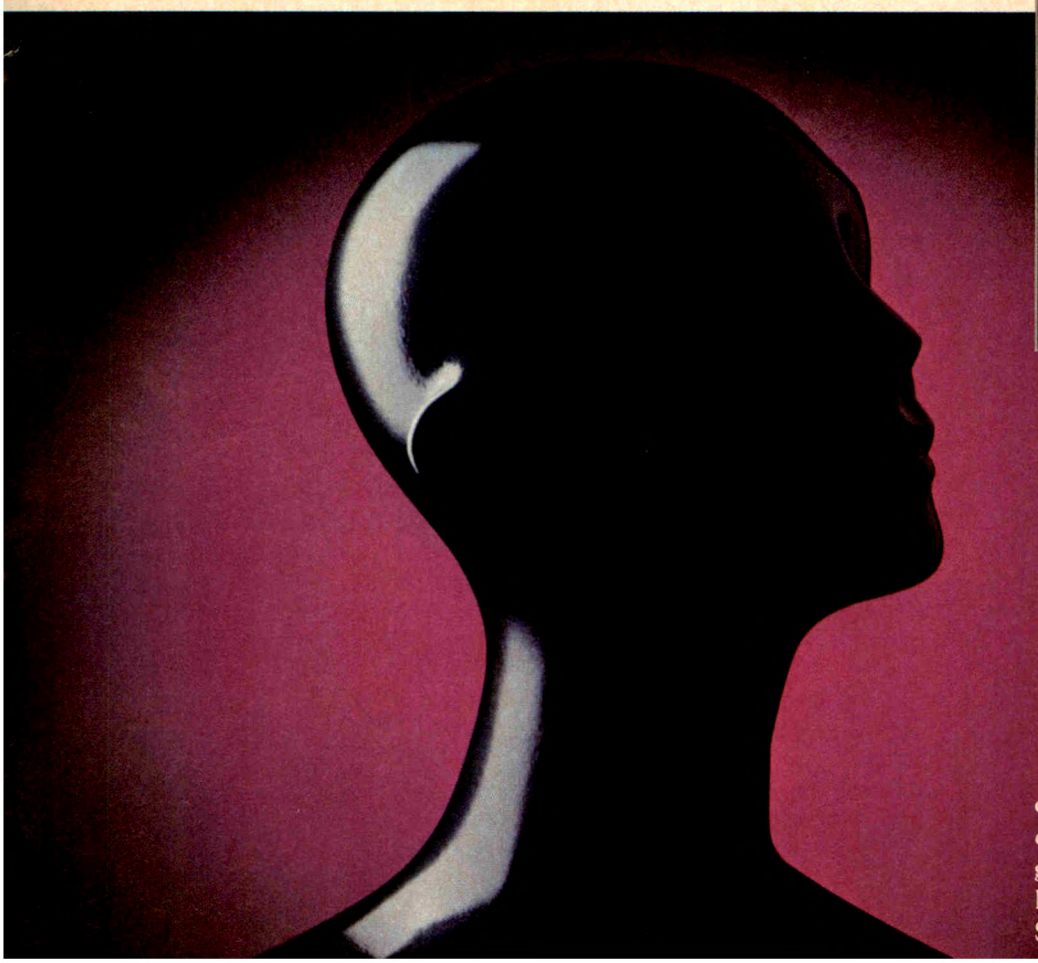

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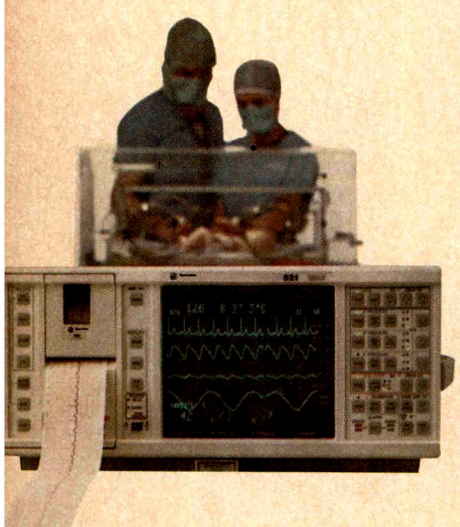

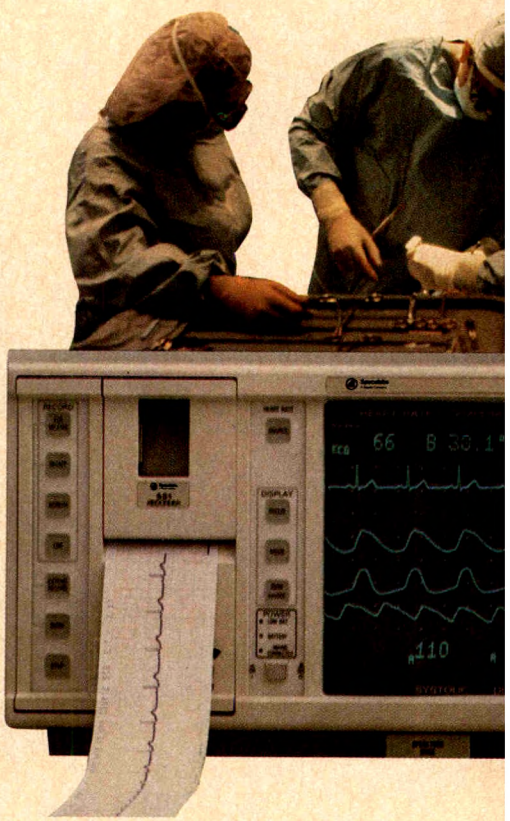

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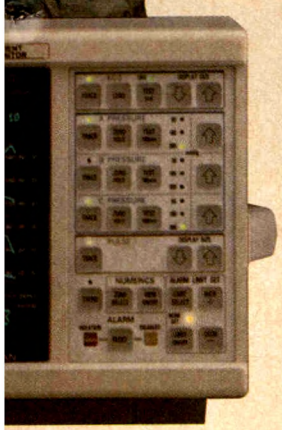

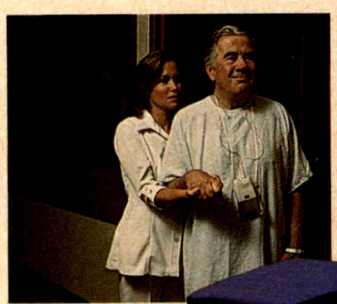

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INDICATIONS—BRETYLOL is indicated in the prophylaxis and therapy of ventricular fibrillation.

BRETYLOL is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS—1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL (bretylium tosylate) should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY—The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN—The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS—1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use of Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function.

ADVERSE REACTIONS—Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

HOW SUPPLIED—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, non-pyrogenic.

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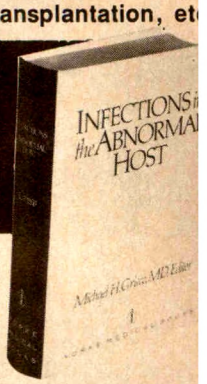

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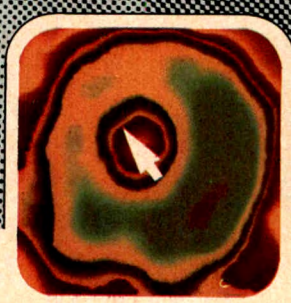
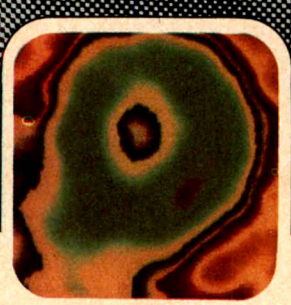


Thallium scintiscan after exercise, showing marked anterior wall perfusion defect (arrow) before angioplasty.[1]



Postangioplasty thallium scintiscan showing no perfusion defect after peak exercise.[1]

FIRST THE BENEFITS OF PRIMARY MEASURES

Never before have physicians had so many resources for dealing effectively with cardiac disease. Now numerous cardiovascular medications are available—antianginal preparations, antihypertensives, diuretics, calcium antagonists, digitalis, quinidine, vasodilators. Besides these many agents, there are proven surgical procedures such as coronary bypass and valve replacement—and nonsurgical procedures such as angioplasty, which is fast becoming an accepted method of treating severe arterial stenoses.[1] The efficacy of angioplasty is illustrated in the above scintiscans. Yet, even with so many primary measures for improving the patient's cardiovascular status, secondary problems may adversely affect convalescence. One such problem may be excessive anxiety.[2]

References: 1. Vawter MH: *Continuing Education 1*/(2):17-24, Aug 1982. **2.** Wenger NK: *Cardiovasc Reviews & Reports 2*:1249-1260, Dec 1981. **3.** Kucharski A: *Am Fam Physician 1*/(3):154-157, Mar 1978.

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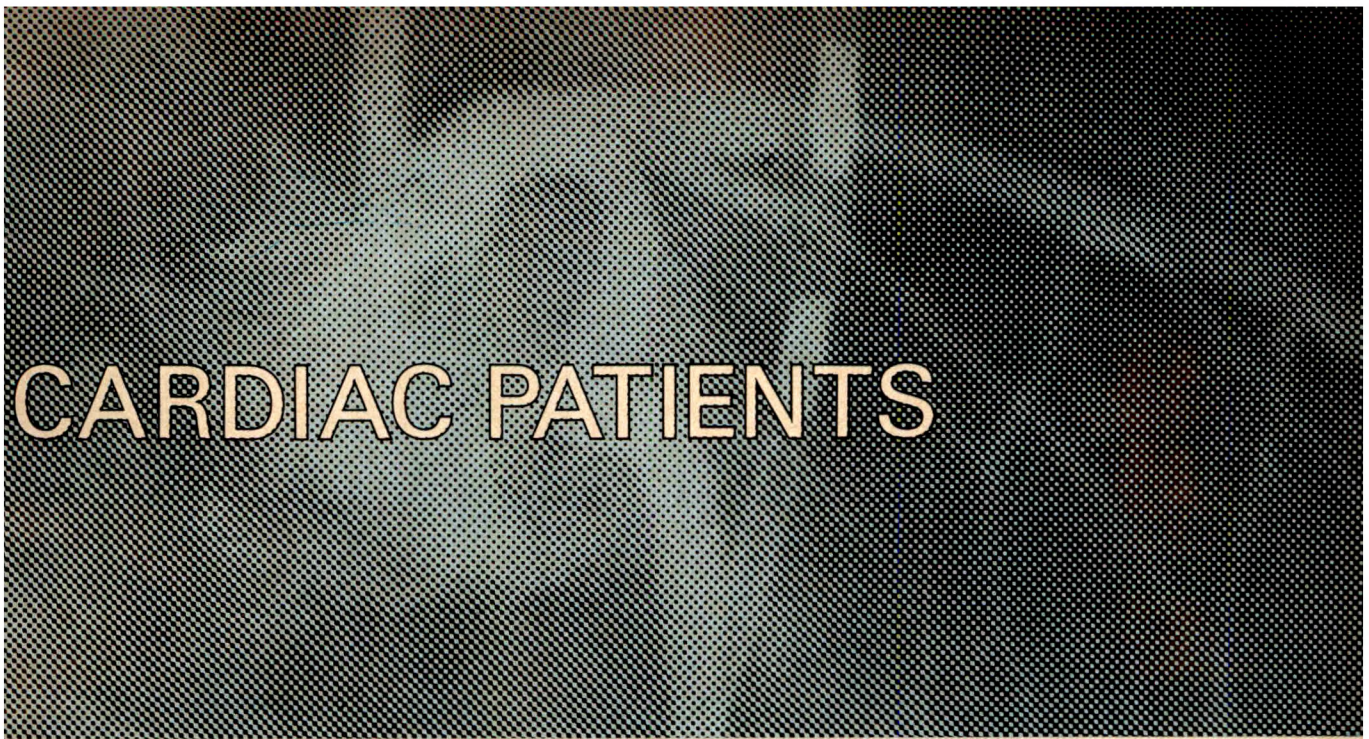

SECOND THE BENEFITS OF ADJUNCTIVE ANTIANXIETY MEASURES

Anxiety in cardiac patients during recovery is a frequent response to symptoms such as chest pain, arrhythmias, breathlessness and weakness.[3] Often, anxiety can be allayed by supportive measures, such as encouraging the patient to express his fears openly, offering reassuring explanations for postcoronary symptoms and, when necessary, prescribing antianxiety medication.[3] For valid reasons, the medication often chosen is Valium® (diazepam/Roche). Its record of efficacy and safety is universally acknowledged. Little or no cardiotoxicity has been reported. Also, Valium is used with most primary cardiac medications. As with all CNS-acting agents, patients should be cautioned against drinking alcohol and against engaging in activities requiring complete mental alertness. Used judiciously, Valium can be a valuable adjunct to rehabilitative measures and can help the cardiac patient employ his own coping devices to good effect.

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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. or q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500; Prescription Paks of 50, available in trays of 10. Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10.

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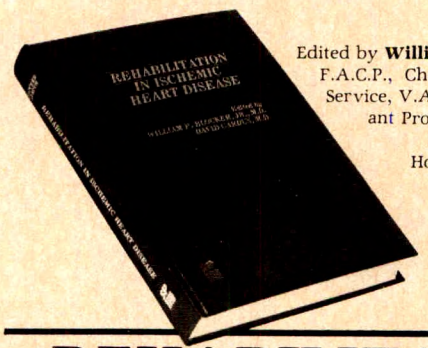

Edited by **William P. Blocker, Jr., M.D.**, F.A.C.P., Chief, Rehabilitation Medicine Service, V.A. Hospital, Houston, Assistant Professor of Physical Medicine Baylor College of Medicine Houston, and **David Cardus** M.D., F.A.C.C., Professor of Physiology and Rehabilitation Baylor College of Medicine, Houston, Texas

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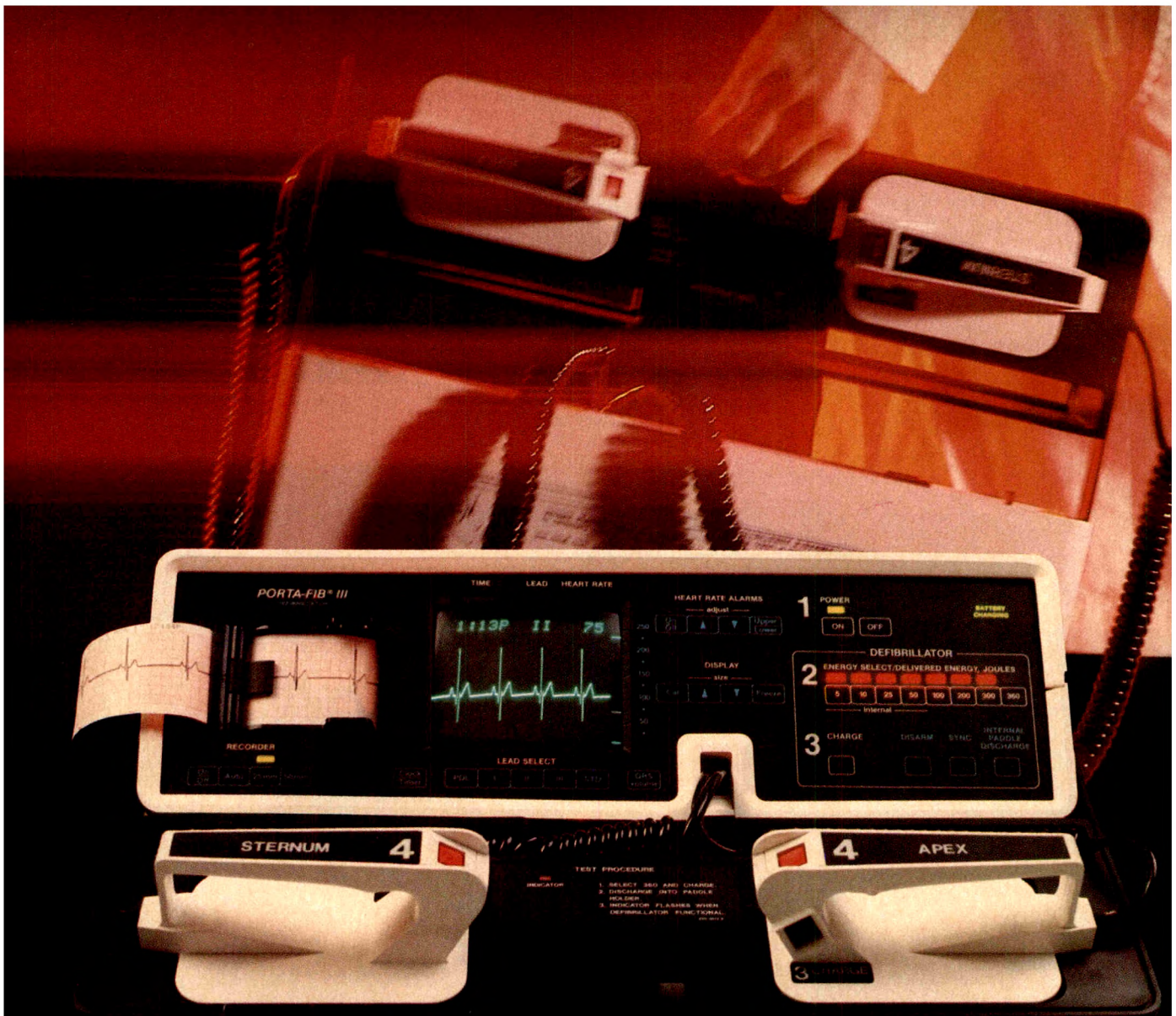

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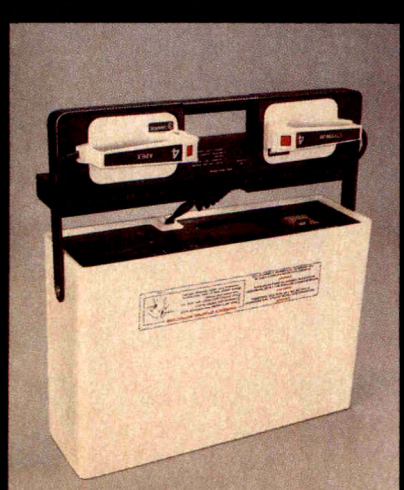

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Prescribing Information

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications**, **Warnings**, and **Precautions**.

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings**.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

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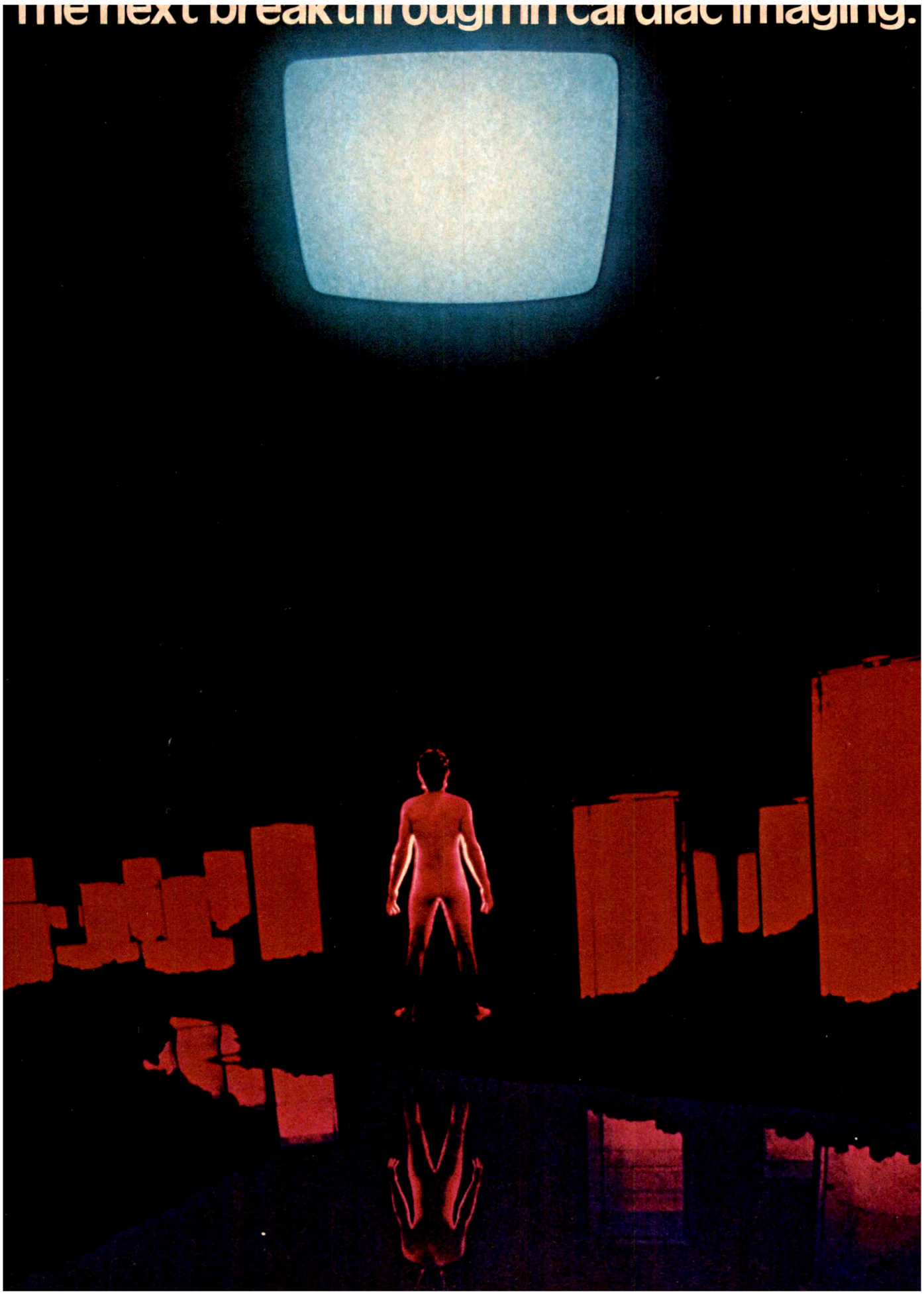
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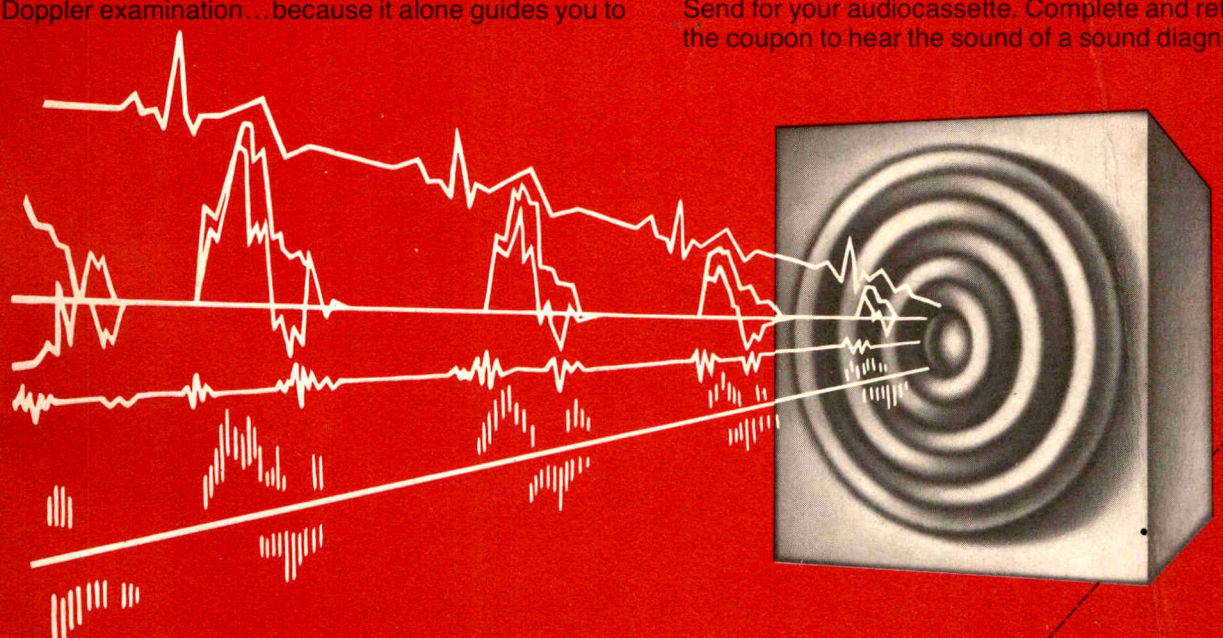

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David T. Kelly, Guest Editor

Preface

DAVID T. KELLY, MB, FRACP

The National Heart Foundation of Australia sponsors a conference every 3 years. Formerly, these meetings were oriented toward a basic bioscience theme and attracted cardiovascular researchers rather than practicing cardiologists.

This 6th triennial conference examined the physiologic and pathologic aspects of the coronary circulation and coronary heart disease. This topic was chosen to provide a forum whereby scientists and practicing cardiologists could discuss areas of research in coronary heart disease and promulgate its importance.

The National Heart Foundation of Australia is a major sponsor of cardiovascular research in Australia. The money for this is raised by voluntary contributions from a public that is ever-increasingly aware of the major effects of coronary disease on its way of life and, indeed, life itself. Unfortunately, there is a paucity of research in coronary disease in Australia. A major aim of this conference was to highlight the areas of research and emphasize that it should be actively promoted in Australia.

Prostanoid metabolism is of ever-increasing importance in the pathophysiology of coronary disease, especially relative to coronary vasomotor changes and arterial thrombosis. Both thrombosis and spasm were discussed extensively on the second day of the meeting, as were the current knowledge of prostanoids on the cardiovascular system and vasospasm.

Much of the clinical research in coronary disease is now in the assessment and management of the patient with acute myocardial infarction. This topic and the results of intracoronary thrombolysis in acute infarction were discussed on the last day of the conference, as was the impact that both beta blockade and calcium antagonist therapy have made on management in myocardial infarction and angina.

A conference on coronary heart disease would be incomplete without mention of coronary artery surgery because of its influence in patient management and in the broader social implications of delivery of health care. In Australia all patients who have coronary artery surgery are registered and the results are analyzed by a committee of the National Heart Foundation. Such data on surgical trends for a whole country is difficult to obtain, and this unique experience is presented.

Atherosclerosis—Relationship to Coronary Blood Flow

ROBERT W. WISSLER, MD, PhD, and DRAGOSLAVA VESSELINOVITCH, DVM, MS

Human atherosclerotic plaques in coronary arteries consist of a variable mixture of lipids, cells and fiber proteins synthesized by the cells. The 2 major space-occupying components of the advanced lesions, which together obstruct the lumen, are the fibrous cap and the necrotic core from which the lesions derive their name. The smooth muscle cells, which make up most cells of the plaque, including the fibrous caps, are produced by migration from the media as well as by proliferation of these cells in the intima. The lipids, mostly supplied by circulating lipoproteins, are present not only in the atheromatous acellular core, but also in the cytoplasm of the cells of the lesion and extracellularly, often attached to 1 or more constituents of the fibrous matrix of the plaque (collagen, elastin and proteoglycans).

In both human and rhesus monkey coronary arteries, the lumen becomes more stenotic as the plaque becomes larger and enlarges as the plaque becomes smaller in response to lipid-lowering therapy. Recent studies in other nonhuman primate models of advanced atherosclerosis have questioned the influence of the plaque lesion on coronary blood flow. For example, in the cynomolgus species of macaque (*M. fascicularis*), depending on how the plaques are induced, the artery lumens may dilate as the plaques become larger because the outside diameters of the arteries increase. Furthermore some diseased arteries are found to stenose further when the animals with advanced coronary plaques are treated by measures that substantially reduce the lipids in the plaques.

Questions now being studied in several animal models and in human arteries include the relative influence of the degree of medial involvement, of lesion cell types, and of lesion circumferential localization (concentric versus eccentric) on these paradoxical phenomena.

Coronary artery atherosclerosis in humans is mostly a disease of the proximal 6 to 8 cm of the major coronary arteries. The lesions, which usually present as intimal plaques, consist of a variable mixture of lipids (including cholesterol and cholesteryl esters), cells and fiber proteins synthesized by the cells. The 2 major space-occupying components of the fully developed plaque, which together can lead to severe stenosis of the lumens of these arteries, are the fibrous cap and the necrotic atheromatous core from which the lesions derive their name (Fig. 1).

The smooth muscle cells, which make up most cells of the human plaque including the fibrous cap, are presumably the product of immigration of cells from the media, accompanied or followed by excessive proliferation (mitosis) of these cells in the intima (Fig. 2). The lipid-cholesterol mixture appears to be mostly supplied by circulating lipoproteins that traverse the endothelial "barrier" and are deposited. This cholesteryl ester-rich lipid is found not only in the atheromatous acellular core, but also in the cytoplasm of the smooth muscle cells, and to a variable extent in macrophages and extracellularly, often attached to 1 or more constituents of the fibrous cap (collagen, elastin or proteoglycans). The fiber proteins of the plaque are largely the product of these proliferated smooth muscle cells.

The space-occupying features of the growing plaque which result in stenosis, are responsible for much of the decrease in coronary blood flow that leads to ischemic heart disease. Nevertheless, many of the acute catastrophic episodes that we call "heart attacks" are triggered by the severe coronary plaques that are often ulcerated or that present a ruptured or torn fibrous cap (Fig. 3). This, in turn, promotes mural or obturating thrombosis or promotes spasm of the major coronary artery superimposed upon or alongside a major plaque that is ulcerated.

The forces that favor occlusion or promote fatal arrhythmias or classic myocardial infarction are opposed

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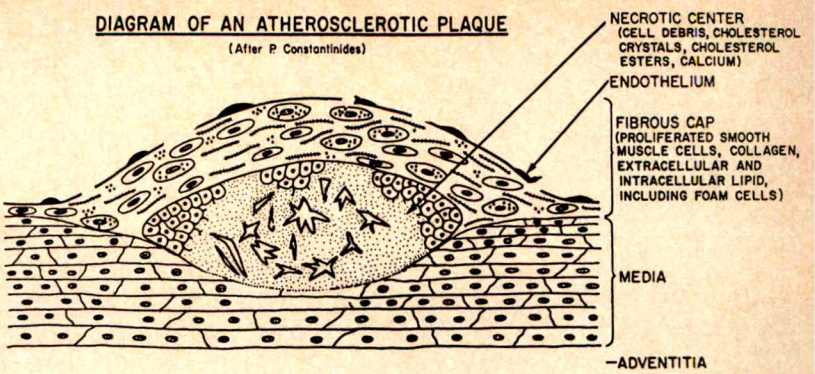

FIGURE 1. The major components of an advanced atherosclerotic plaque, including the grumous necrotic center from which the lesion derives its name and the fibrous cap made up largely of lipid-filled smooth muscle cells and fiber proteins produced by these cells, mainly collagen and elastin. The evidence of injured endothelium is a common feature of the advanced plaque.

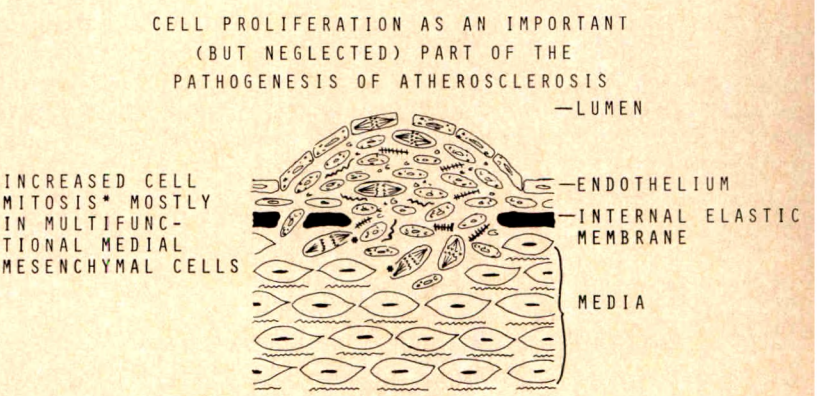

FIGURE 2. Arterial smooth muscle cell migration (from the underlying media) and active proliferation in both the intima and the media as important components of atherogenesis in human and nonhuman primate atherogenesis. LDL = low-density lipoprotein. Modified from Wissler RW. In: Homburger F, ed. Comparative Pathology of the Heart. Basel: S. Karger, 1974:10–31.

to a variable extent, by coronary artery collaterals[1] and by dilation of severely diseased arteries.[2] Weakening of the media and enlargement of the entire circumference counteract stenosis, as reflected by morphometric evaluation of the external elastic membrane.

The stenosing tendencies of the plaque are also strongly opposed in most humanoid animal models, and probably in humans with advanced disease as well, by an effective set of reactions that occur when the lipid levels in the blood are lowered to levels often observed in most adults in populations where atherosclerosis usually does not progress and ischemic heart disease is rare. This evidence of decrease in lesion size (regression), healing of endothelium and remodeling of the fibrous cap has been well documented in numerous quantitative studies of regression of advanced atherosclerosis in macaques, dogs and swine.[3–8]

This presentation documents and evaluates some recent human clinical-pathologic and experimental pathophysiologic data that support the concept of these opposing forces involved in progression, healing and regression.

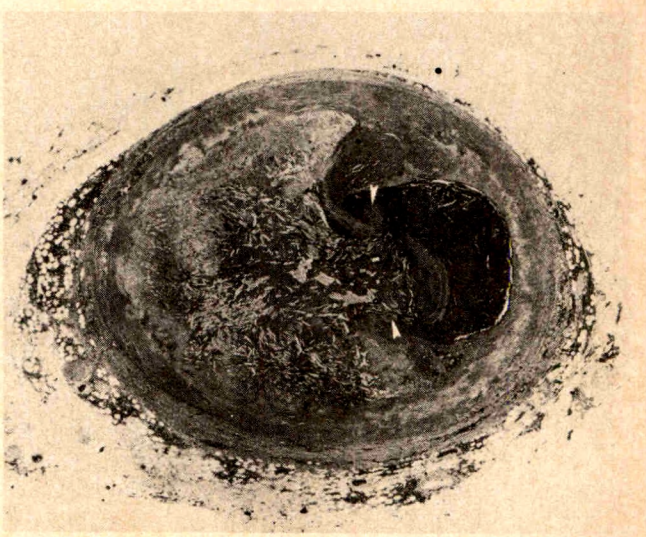

FIGURE 3. Photomicrograph from an occluded coronary artery in which the thrombosis appears to be directly related to a ruptured fibrous cap over a very severely diseased plaque, which has a large necrotic, cholesterol-rich core. Reproduced from Buja LM, Willerson JT. Am J Cardiol 1981;47:343–356, with permission of the publisher.

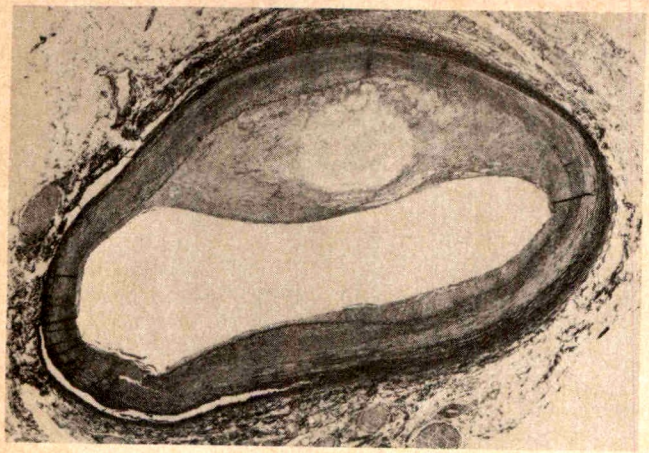

FIGURE 4. Coronary artery plaque from a 54-year-old man who was found to have subendocardial myocardial necrosis when he died, about 12 hours after acute onset of chest pain. The lesion, a prototype of many observed at autopsy and probably not detected by angiography, is characterized by a thin, loose, fibrous cap and a proportionately larger necrotic center.[9]

New Data on Plaque Progression

Roberts[9] studied severe atherosclerotic plaques from human autopsies and recognized that the mass of the plaque may not be as important as the relative quantities of components in triggering a clinical event. For example, many relatively small, eccentric plaques, each with a very lipid-rich center and a very thick fibrous cap, have been shown that could not be detected with angiography. These soft and "florid" plaques are dangerous because of their propensity to "fibrous" cap rupture and platelet adherence, resulting in thrombosis or coronary spasm (Fig. 4).

Roberts[10] proposed patterns of stenosis and described eccentric and concentric plaques. Two examples of advanced concentric and eccentric coronary lesions in the human are shown in Figure 5.

Our observations in rhesus monkeys and cynomolgus monkeys using identical atherogenic rations in our laboratory have suggested a new interpretation of eccentric versus concentric lesions (Fig. 6).

The cynomolgus monkey regularly develops co centric coronary lesions, but the same diet fed to th rhesus monkey (Fig. 6) almost exclusively produc eccentric coronary lesions. These cynomolgus lesio often display a large proportion of mononuclear cell many of which are converted to foam cells. The foa cells are not only intimal but often become concentr cally transmural with extensive destruction of th media. In numerous instances, the adventitia is als extensively involved. These atheromatous lesions r semble the transmural lipid-rich lesions seen in som patients with incompatible human heart transplants c those produced experimentally by Alonso et al[11] i homologously transplanted animals and Minick e al[12,13] in rabbits with serum sickness (both groups re ceived an atherogenic ration). These lesions resembl those seen in hypercholesterolemic subjects who als have immune complex panarteritis.

When findings in rhesus and cynomolgus monkey were compared with those from our laboratory, over 80 of cynomolgus monkeys had definite evidence or ci culating Ag-Ab complexes, but rhesus monkeys di not.

We believe that this widespread concentric and ofte highly destructive lesion in cynomolgus monkeys i different from most coronary lesions in humans an may explain why regression is uncommon.[8,14,15] Othe investigators have observed different regression pat terns in cynomolgus lesions under conditions tha consistently lead to regression of advanced atheroscle rosis in the rhesus species of macaques (*Macaca mu latta*). These transmural lesions, with their smolderin medial inflammation, form scars that constrict whe they lose their lipids. Malinow et al[16] reported an ex ception. Using a less atherogenic ration and a short in duction, these workers reported substantial regressio resulting from incorporation of either alfalfa meal o cholestyramine in the slightly modified atherogeni ration.

Bond et al[2] reported that this lesion produces mor dilatation of the artery, as measured by the increase ir diameter or circumference of the internal elasti membranes during induction, than they observed ir rhesus monkeys (Table I) and that this may alter cor onary flow. Vesselinovitch and Wissler[17] showed a

TABLE I Plasma Lipid and Coronary Artery Size Characteristics*

	Baseline (19-Month Progression)	24-Month Regression		48-Month Regression	
		High TPC	Low TPC	High TPC	Low TPC
Number	18	18	18	18	18
TPC†	777 ± 36	302 ± 8	194 ± 4	316 ± 10	202 ± 4
IEL area	1.08 ± 0.10	1.31 ± 0.16	1.35 ± 0.16	1.80 ± 0.12	1.80 ± 0.09
Intimal area	0.30 ± 0.06	0.44 ± 0.08	0.26 ± 0.08	0.29 ± 0.07	0.21 ± 0.05
Luminal area	0.78 ± 0.07	0.87 ± 0.10	1.09 ± 0.12	1.51 ± 0.09	1.60 ± 0.07
Percent stenosis	28	34	19	16	12

Adapted from Bond et al.[2]
* Area measurements are expressed as millimeters squared (mean ± standard error of the mean).
† Total mean plasma cholesterol concentration (mean ± standard error of the mean).
IEL = internal elastic luminal; TPC = total plasma cholesterol.

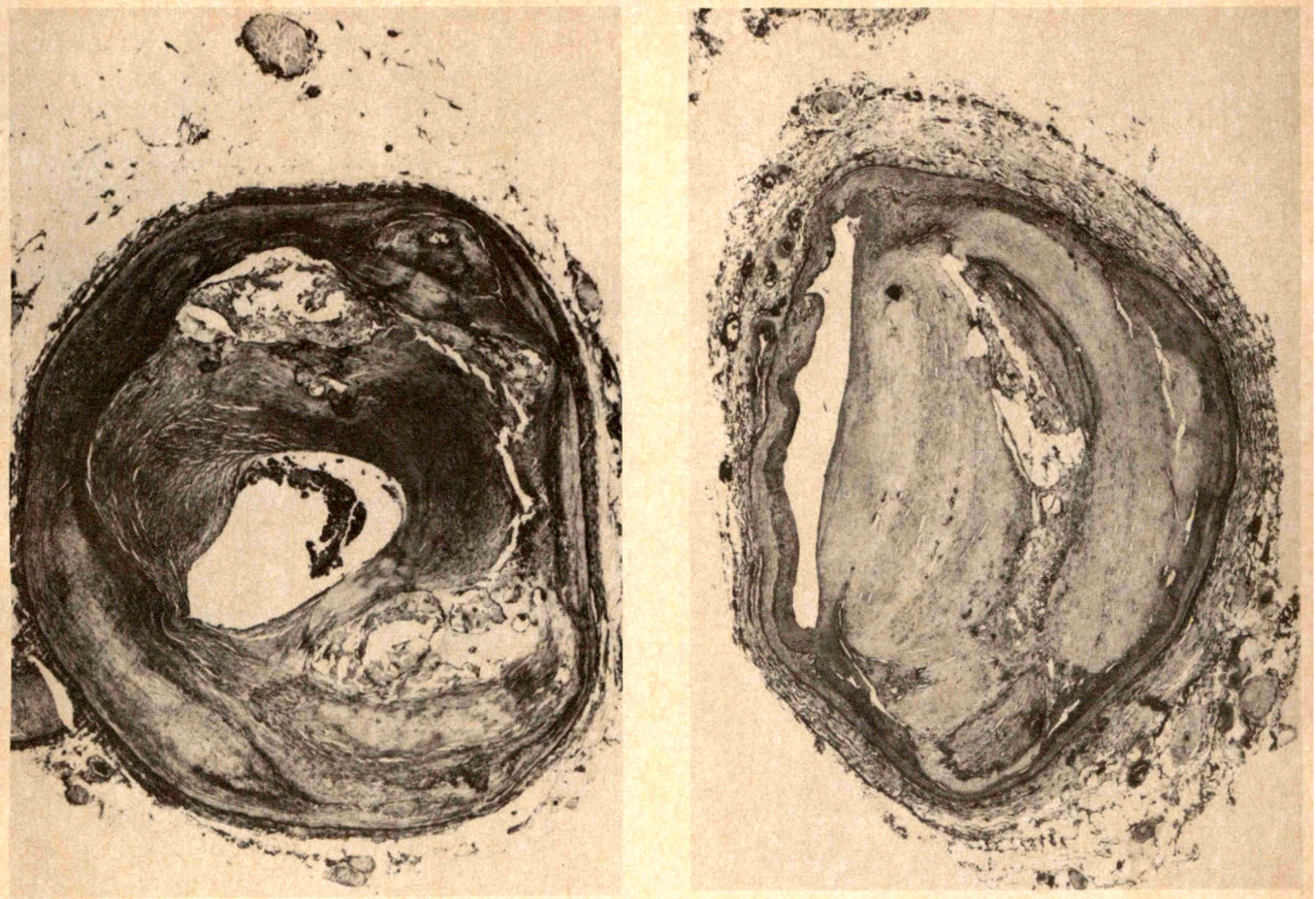

FIGURE 5. Photomicrographs of concentric and eccentric lesions in coronary arteries, which illustrate much more medial involvement and medial degeneration and atrophy in the concentric lesion. Note the intact media opposite the eccentric lesion. Reproduced from Roberts[9] with permission of the publisher.

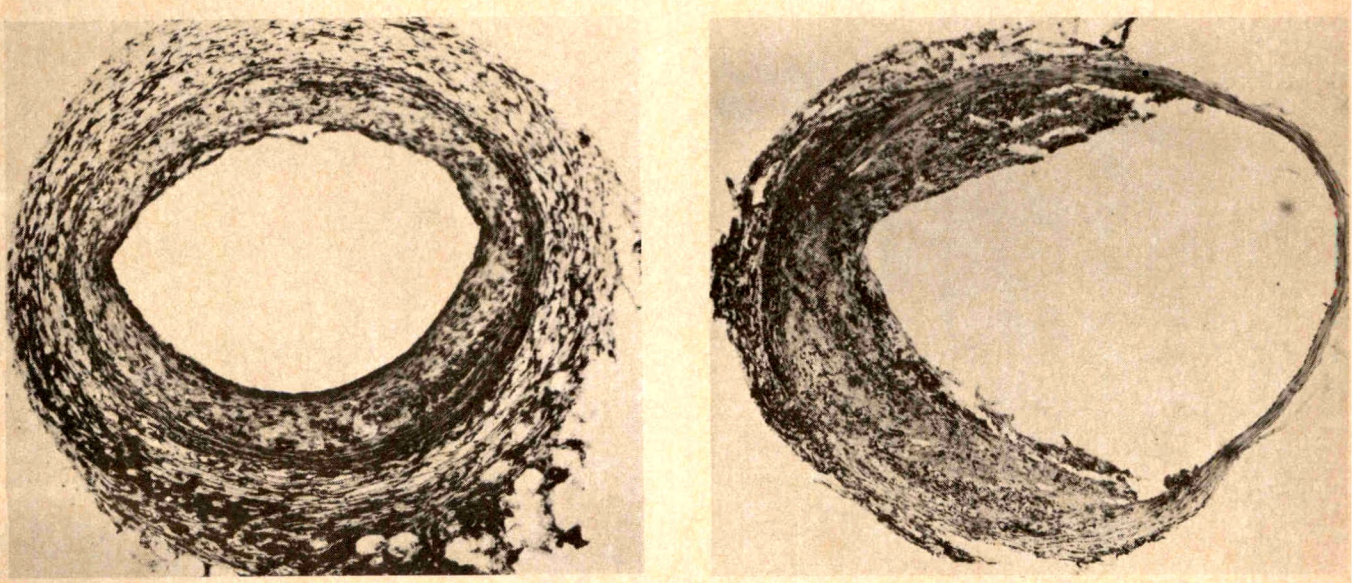

FIGURE 6. Advanced plaques from a recent experiment.[17] **Left,** lesion stained with a fat stain, is a typical concentric lesion, with abundant destructive medial involvement and extensive adventitial foam cell infiltration. **Right,** a typical rhesus lesion with an advanced eccentric plaque showing a necrotic center and very little damage to the arterial medial musculature except in small focal areas.

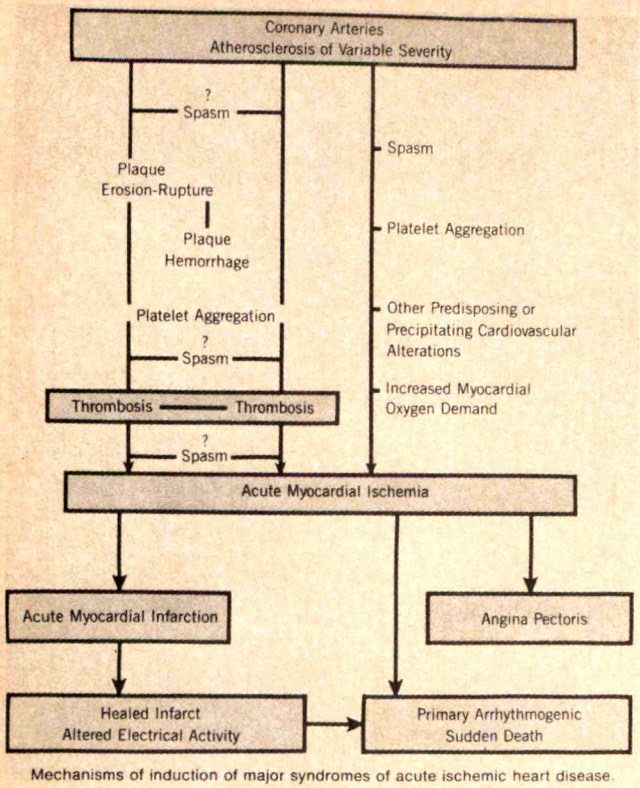

FIGURE 7. The two types of pathogenetic sequences, each of which may account for about half of the heart attacks in the United States. Reproduced from Buja et al[18] with permission of the publisher.

definite arterial dilatation in cynomolgus monkeys but no change as the lumen filled in with plaque in the adult male rhesus monkeys. These observations may be clinically important because concentric coronary lesions, with extensive medial destruction or atrophy, are occasionally seen in humans, and may be detected by noninvasive techniques and differentiated from the usual eccentric intimal coronary plaque.

Concentric transmural medial lesions should be associated with greater dilation of lumens during atherogenesis[2] and less decrease in stenosis during regression.[14,15,17] The concentric lesion may be less likely to be associated with vasomotor change.[18] The more usual eccentric lesions would not increase the outside diameter of the artery during progression, except that those which accompany growth would be associated both with a more effective regression with less fibrous replacement of the media and with restoration of the original lumen. The intact media away from the plaque may develop spasm due to the greater preservation and availability of smooth muscle cells.

A recent review[18] suggests that a disrupted intimal over a soft (but not necessarily angiographically visible) plaque may be important in the pathogenesis of coronary spasm. This suggests a dual pathogenesis of clinical event (Fig. 7), both associated with severe atherosclerosis, 1 associated with spasm and 1 with thrombosis.

Figure 7 illustrates the probable pathogenetic sequence[18] and shows agreement with the findings of other investigators.[19,20]

Increased levels of catecholamines during stressful episodes or those liberated from platelets spread over ulcerated or partially denuded atherosclerotic plaques may trigger vasomotor changes. Coronary spasm, which could be the missing link of the chain, is such a common cause of acute heart attacks due to sudden onset of arrhythmia.

New Data on Plaque Regression

Atherosclerosis in humans[21,22] and in the rhesus monkey model[23,24] can be partially reversed; studies suggest that a small decrease in an advanced obstructive plaque could greatly increase coronary blood flow. In chronic hypercholesterolemic animals, when serum cholesterol level is lowered the damaged endothelium is repaired. The atherosclerotic plaques may not cause platelets to stick and release vasoactive amines.[25,26] The changes that occur in experimental studies of regression in the rhesus monkey are shown in Figure 8.[27] In humans, Barndt et al[28] documented that regression occurs in patients who have lowered their serum cholesterol levels substantially in contrast to those who could not.

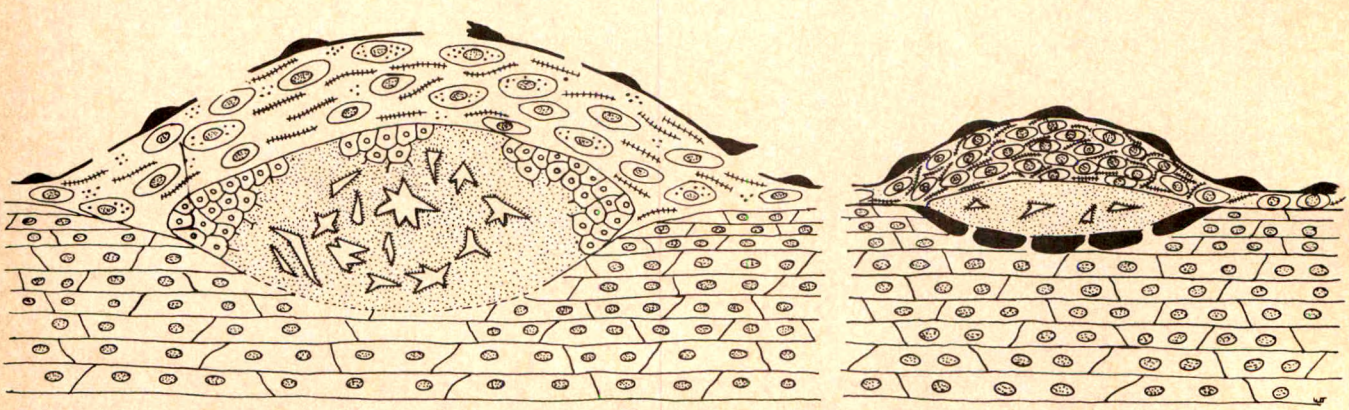

FIGURE 8. The major changes observed in quantitative studies of plaque regression in several species of experimental animals. **Left,** a typical advanced plaque. The main features usually seen in this process (**right**) are healing of endothelium, a substantial decrease in size and lipid cholesterol content of the necrotic center, a marked reduction in intra- and extracellular lipid in the fibrous cap, and condensation of the fiber proteins in this part of the plaque; as a result of these changes, the plaque size is reduced. Reproduced from Barndt et al[28] with permission of the publisher.

Similarly, Bevans et al[3] reported that sequential coronary arteriograms may show regression of atherosclerosis a year or 2 after partial ileal bypass therapy when patients have significantly lowered serum cholesterol and low-density lipoprotein values.

Our present knowledge of the mechanisms by which coronary atherosclerosis produces its effect on coronary blood flow suggests that regression of plaque size would occur in those persons who have a sustained lowering of their serum lipid levels.

Future Prospects

In the animal models such as *Macaca mulatta*, whose advanced plaques resemble human atherosclerosis most closely, the same type of stenosing lesions as those in humans are found and various therapeutic regimens can be tested. Effects of therapy over time on coronary flow and lesions can be studied. In the experimental model, these results can be validated in vivo by highly quantitative morphometric observations made in postmortem specimens.

The large, cumbersome, often complex mass clinical trials in humans, with their end points of mortality or myocardial infarction, can be replaced by evaluation of intervention using direct noninvasive imaging and Doppler flow techniques. These can be monitored by quantitative morphometric techniques applied to the human autopsy specimens of the same coronary arteries. These approaches are being explored in both experimental animals and human carotid and femoral arteries.[29]

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Local Factors Controlling Coronary Circulation

DAVID E. L. WILCKEN, MD

Mechanical, metabolic, anatomic and, possibly, myogenic factors contribute to the local regulation of coronary blood flow. The hindrance to flow produced by systole can easily be quantitated, but the measurement of diastolic pressure-flow relations in the different layers of myocardium poses problems. The coronary circulation is an autoregulated vascular bed, and failure of autoregulation produces subendocardial ischemia. Flow is almost entirely diastolic and the available evidence suggests that variations in diastolic extravascular pressure across the myocardium result in a series of waterfall effects; these extravascular pressures are highest in the endocardium and decrease progressively toward the epicardium. This hypothesis would explain subendocardial ischemia with reduced diastolic perfusion pressures when the coronary circulation is maximally vasodilated.

Metabolic factors produce large changes in coronary flow and flexibility in adjusting oxygen supply to need. Present data suggest an important role for adenosine as a vasodilator mediator. Considering the importance of metabolic vasodilatation for normal cardiac function, a unitary theory of regulation with a single vasodilator would lack built-in safety factors and flexibility; it is unlikely that there is a single mediator for every kind of physiologic coronary vasodilatation. Evidence is accumulating for interrelations between naturally occurring coronary vasodilators, with important links provided by prostaglandins, and for intrinsic changes in vascular smooth muscle function contributing to postocclusion hyperemia.

Changes in vascular smooth muscle function alter flow within limits dictated by coronary anatomy. The wide anatomic variation between individual subjects is consistent with the importance of genetic factors in determining the anatomic characteristics of the coronary vascular tree, and the effect these will have on myocardial perfusion, particularly in pathophysiologic states.

Three basic phenomena determine resistance to blood flow in the coronary circulation: the mechanical effect of the beating heart, the contractile activity of the smooth muscle cells in the walls of the coronary vessels, and the anatomy of the coronary vasculature and its collateral circulation. The first produces a mechanically determined hindrance to coronary flow unrelated to any intrinsic control of coronary conductance; the second is under the control of both the cardiac nerves and local metabolic processes of the heart. In the third, the differences between individuals and between species are presumably genetically determined, but accentuated by varying myocardial oxygen requirements and the presence of myocardial ischemia. This study examines some recent developments, touching upon each of these 3 determinants of coronary vascular resistance or its reciprocal conductance.

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Extravascular Coronary Resistance

Downey[1] reviewed changes in coronary conductance the heart itself produces by compressing coronary vessels during systole, and thereby increasing resistance to flow. Sabiston and Gregg[2] established that this is indeed the case beyond doubt 25 years ago when they measured right and left coronary artery flow in dogs at constant perfusion pressure before and after temporary asystole produced by vagal stimulation; with the onset of asystole there was always a dramatic increase in coronary blood flow. They showed that in the normal heart, one third to one half of total coronary resistance is extravascular in origin, and that this is almost certainly due to systolic compression of coronary vessels. It is difficult to obtain absolute values for tissue pressure during systole so as to quantitate transmural extravascular systolic forces. Nevertheless, the findings in these early experiments, and many related ones subsequently, provide an adequate explanation for left

ventricular coronary flow being almost entirely a diastolic phenomenon. Indeed, recent data suggest that flow recorded in systole (about 20% of the total) remains in superficial distensible conducting vessels and that subendocardial flow is entirely diastolic.[3,4] Since the subendocardial region of the left ventricle is the area most vulnerable to ischemic damage, an important immediate question is: What effects do the mechanical events of the cardiac cycle have on diastolic perfusion?

Hoffman and co-workers[5,6] approached this in the following way: they proposed that flow per beat is in proportion to the diastolic pressure-time index (DPTI), defined as the area between the ventricular pressure and the aortic pressure during the diastolic period; and that the metabolic requirements per beat were dictated by the area under the systolic pressure-time index (SPTI) as described by Sarnoff et al.[7] The ratio of DPTI/SPTI was then used as an index of the supply-demand status of the myocardium. They plotted the DPTI/SPTI against measurements of regional myocardial blood flow, determined by the distribution of injected radioactive microspheres, in experiments that reproduced the hemodynamic changes found in clinical situations. The results are summarized in Figure 1. This figure shows that there is normally an even distribution of flow between epicardium and endocardium, the ratio DPTI/SPTI is normally approximately 1, and interventions that lower the ratio to about 0.5 result in a progressive reduction in endocardial flow relative to epicardial flow.

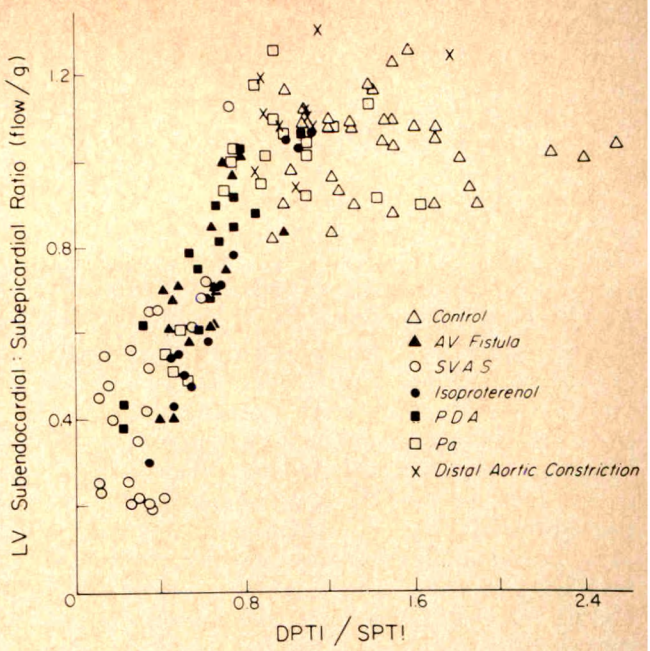

FIGURE 1. The reaction between DPTI:SPTI (ratio of diastolic pressure-time index to systolic pressure-time index) to subendocardial: subepicardial flow in anesthetized dogs in different experiments that mimicked clinical situations (see text). Subendocardial flow decreases relative to subepicardial flow with pressure ratios below about 0.6. AV = arteriovenous; Pa = pacing; PDA = patent ductus arteriosus; SVAS = supravalvular aortic stenosis. Reproduced from Hoffman[6] with permission of the publisher.

The coronary circulation is an autoregulated vascular bed so that, for a given myocardial oxygen demand, coronary blood flow remains relatively constant over a wide range of imposed perfusion pressures.[8,9] The experiments of Hoffman et al[5,6] suggest that autoregulation extends into the various layers of the left ventricle, which have different systolic, and presumably diastolic, tissue pressures, and that autoregulation persists despite major pressure and flow changes. It follows that there are powerful mechanisms operating in the myocardium to maintain even transmural perfusion. This is well illustrated by the experiments in dogs by Rouleau et al,[10] who kept myocardial oxygen requirements constant and determined the effect on regional myocardial blood flow of altering coronary perfusion pressure. Even transmural perfusion was maintained over a wide range of pressures, but when a breakdown in transmural autoregulation did occur, it always resulted in subendocardial ischemia. Subendocardial ischemia occurs when autoregulating mechanisms produce maximal coronary vasodilatation so that subendocardial flow becomes entirely dependent upon perfusion pressure;[10] a further decrease in perfusion pressure then results in subendocardial ischemia.

The reasons for subendocardial vulnerability to ischemia are obviously important. Two major reviews have considered this question recently.[1,11] A superficial view might be that as the subendocardium is perfused only in diastole, it is simply at the end of the line for a flow system perfusing from the epicardial surface of the heart to the endocardium. Yet there is good evidence that endocardial conductance is greater than that for the epicardium,[10,12,13] and there is also mounting evidence for the importance of waterfall effects occurring in the coronary circulation and influencing diastolic perfusion.

The waterfall hypothesis was suggested by Holt[14] and has been shown to be important in other regional circulations, particularly in the lung.[15] If, as seems likely, small coronary veins act like collapsible tubes passing through relatively rigid heart muscle, conditions in the myocardium are analogous to those produced by a Starling resistor.[16] The difference between diastolic inflow pressure and diastolic extravascular or tissue pressure will determine diastolic flow if the tissue pressure is higher than that in the right atrium. Downstream pressure will not affect diastolic flow as long as it is lower than the diastolic extravascular tissue pressure compressing collapsible upstream vessels. Under these circumstances, if inflow pressure is progressively lowered, flow will stop when inflow and tissue extravascular pressures are the same. Thus, if there are diastolic waterfall effects in the myocardium, pressure at zero flow should equal tissue extravascular pressure. This consideration excludes contributions from inertial forces and the capacitance of the vessels, but these contributions are likely to be small.[1,11]

Bellamy[17] examined pressure-flow relations in conscious dogs at very slow heart rates. He found linear pressure-flow relationships during long diastolic pauses under resting conditions, with a pressure intercept of

about 50 mm Hg. With maximal vasodilatation, the intercept was 15 to 20 mm Hg. This suggests that the pressure intercept at zero flow is affected by vascular tone and that during maximal vasodilatation this pressure may represent the myocardial extravascular pressure.

Reexamination of pressure-flow curves determined in this laboratory in chronically conscious dogs entirely confirmed Bellamy's results in relation both to the linearity of the pressure-flow relationships and the magnitude of the pressure intercept, both under resting conditions and during maximal coronary vasodilatation (Wilcken DEL, unpublished data). Distal coronary artery diastolic pressures after circumflex coronary artery occlusions have been of the same magnitude. In conscious humans, distal coronary artery diastolic pressures at zero flow, determined during complete occlusion of the left anterior descending coronary artery at percutaneous transluminal angioplasty in this institution, have also consistently shown diastolic values of 10 to 20 mm Hg (McCredie RM, personal communication). Although these distal pressures may, in some instances, be influenced by collateral flow, it is nevertheless important to note that in >100 occlusions performed in this institution in dogs and man, distal coronary artery pressures have always been of that order.

The relevance of the waterfall hypothesis to subendocardial ischemia is supported by the finding of Rouleau et al[10] of a higher diastolic pressure intercept for the endocardium than for the epicardium, when intercepts were obtained by extrapolation of linear pressure-flow curves from different layers of the dog myocardium. This same group has provided evidence for a waterfall effect occurring in the coronary sinus.[18] These data suggest that when there is maximal coronary vasodilatation, and flow to the subendocardium then depends only on coronary driving pressure, flow to the endocardium will decrease first because diastolic coronary extravascular pressures are higher there than in the middle and subepicardial layers; therefore, for a given diastolic coronary perfusing pressure, the epicardial driving pressure will be greater than that for the endocardium and, under conditions of maximal vasodilatation, the decrease in subendocardial driving pressure will inevitably result in lower endocardial flow.

Coronary Vascular Smooth Muscle Activity and Conductance

Although extravascular factors are responsible for up to 50% of the hindrance to flow and are largely systolic, contributions from metabolic, neural and, possibly, myogenic factors account for the remainder by changing coronary vascular smooth muscle activity. They introduce flexibility into the system by permitting flow to vary widely in relation to physiologic demands. It may increase 6- or 7-fold above resting levels; there is little doubt that metabolic factors are the most potent mediators of these responses, which are essential for increased oxygen delivery, because of the high oxygen extraction at rest in the coronary circulation (>50%).[9]

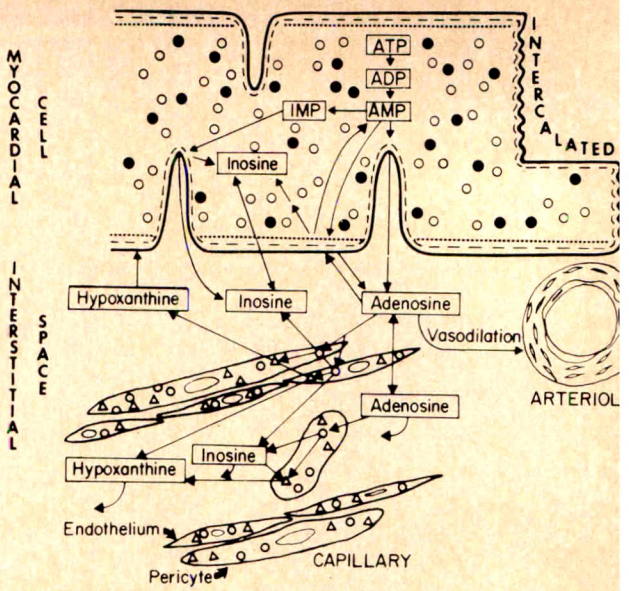

FIGURE 2. The adenosine hypothesis. AMP is formed from the brea down of ATP in the myocardial cell and is dephosphorylated at the ce membrane by 5′-nucleotidase. Adenosine moves into the interstiti space to act on vascular smooth muscle producing vasodilatation reenters the myocardial cell. Any adenosine moving into the bloc stream is deaminated to inosine and hypoxanthine. Reproduced fro Berne and Rubio[9] with permission of the publisher.

Metabolic Regulation

The relationship between myocardial metabolic ac tivity and coronary vessel tone has been reviewed au thoritatively by Parratt.[19] There is a linear relationshi between coronary blood flow and myocardial oxyge consumption[9,19] and a hyperbolic relationship wit coronary venous oxygen content (reflecting myocardia oxygen partial pressure), sharp increases in flow oc curring when coronary venous oxygen content fall below 5 ml/100 ml.[20] Although oxygen itself might hav a direct effect on vascular smooth muscle, it is unlikel that a change in coronary perivascular oxygen tensio alone is the principal mechanism for metabolically in duced coronary vasodilatation. For example, Broadley[2] perfused 2 guinea pig isolated hearts in series with physiologic solution and reoxygenated the effluent fron the donor heart before it reached the recipient heart This latter heart had been pretreated with histamin receptor and adrenoceptor-blocking drugs. Epineph rine, isoproterenol or histamine given to the donor hear produced coronary vasodilatation in the recipient heart so, too, did tachycardia induced in the donor heart by electrical pacing and hypoxia. There was, therefore myocardial release of a stable vasodilator substance o substances producing vasodilatation in the fully oxy genated recipient heart.

A number of vasoactive substances link coronary blood flow to the metabolic requirements of the heart the evidence for and against the various putative cou pling agents has been extensively reviewed.[9,19] Of the candidates for the role of local mediator of metabolic vasodilatation, the most thoroughly researched is adenosine.

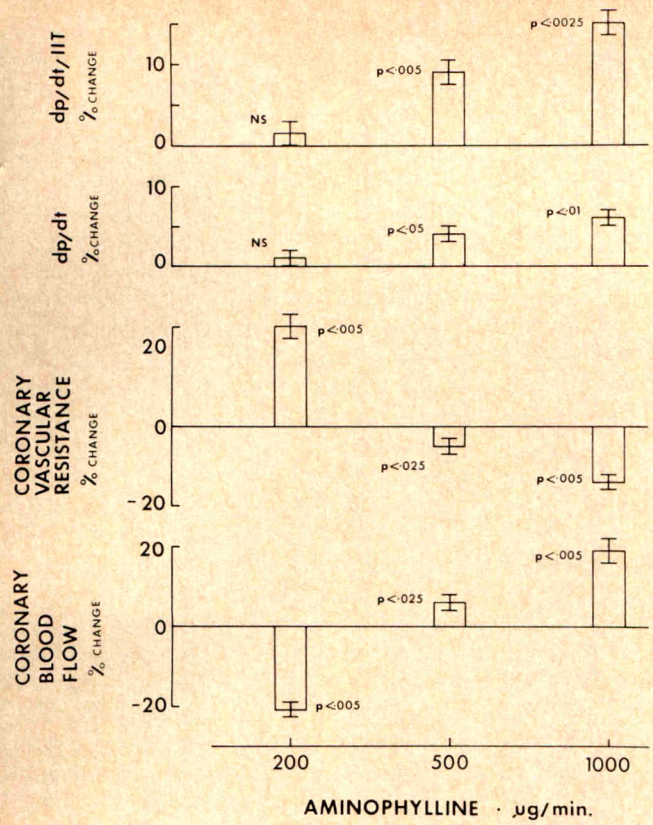

FIGURE 3. The effects of 10-minute close coronary artery infusions of aminophylline on coronary blood flow, coronary vascular resistance and myocardial contractility in a donor dog heart transplanted into the neck of an anesthetized recipient dog (see text). Low-dose infusions reduced coronary flow and increased coronary vascular resistance without changing retractibility, whereas higher doses increased flow contractility. There were no significant changes in donor heart rate or perfusion pressure. Values are mean ± standard error. dp/dt = peak rate of change of donor heart intraventricular pressure; IIT = integrated isometric tension. Reproduced from Paoloni and Wilcken[30] with permission of the publisher.

Adenosine

The development of the adenosine hypothesis has been largely a result of the work of Berne et al, which is summarized in their recent review,[9] from which Figure 2 of the present report is reproduced. Adenosine monophosphate production reflects the degree of adenosine triphosphate utilization and hence the energy state of the cell. The enzyme that dephosphorylates adenosine monophosphate to adenosine, 5′-nucleotidase, appears to be conveniently situated at the cell membrane, in the T tubules, and in the cells surrounding capillaries, the pericytes. Adenosine moves quickly through cell membranes into the interstitial space. There it may dilate arterioles and enhance oxygen delivery, which then reduces the production of adenosine monophosphate and of adenosine. Additional adenosine may reenter the cell or be deaminated in red cells by adenosine deaminase.

Adenosine fulfills many of the conditions required for it to be a metabolic coupling agent linking coronary blood flow to myocardial oxygen demand. It is present in measurable concentrations in the heart and in amounts related to myocardial oxygen requirements; levels change significantly even during a single cardiac cycle.[22] It can be detected, together with its metabolites, in coronary venous blood specimens from humans during myocardial ischemia induced by pacing.[23] In a variety of animal experiments there has generally been good correlation between the degree of coronary vasodilation and the amount of adenosine released.[9,19,24] There is convincing evidence that adenosine acts on a receptor at the smooth muscle cell surface in that high-molecular-weight adenosine derivatives and protein-AMP conjugates that are too large to enter cells and are not inactivated by adenosine deaminase show the same coronary vasodilator activity as adenosine.[25–27]

The principal problem with the adenosine hypothesis has been that drugs that antagonize or potentiate adenosine-induced coronary blood flow responses should modify flow responses to increased myocardial oxygen demand; the experimental data reveal conflicting results. Aminophylline inhibits competitively the coronary vasodilator actions of adenosine.[28,29] Studies from this laboratory showed that low-dose close coronary artery infusions of aminophylline in a transplanted dog heart model, similar to a Langendorff preparation, reduced coronary blood flow at constant perfusing pressure without altering myocardial contractility or heart rate (Fig. 3).[30] Higher doses increased coronary blood flow and myocardial contractility without changing the heart rate. Alpha-adrenoceptor blockade did not affect the low-dose vasoconstrictor response in this isolated heart preparation. A similar biphasic coronary blood flow response to aminophylline has also been shown recently in conscious dogs,[31] but the low-dose vasoconstrictor effect appeared to be alpha-adrenoceptor–mediated. Thus, although we had no direct proof that adenosine blockade was responsible for the low-dose coronary vasoconstrictor response in our preparation, it could have been produced by inhibition of the vasodilator action of locally produced adenosine and therefore consistent with the adenosine hypothesis.

There have been many studies reporting the effects of adenosine potentiating (dipyridamole and lidoflazine) and inhibiting (theophylline and aminophylline) agents on myocardial reactive hyperemia. Although earlier results were conflicting, more recent findings are consistent and have been summarized.[19,24] Drugs which profoundly alter adenosine-induced vasodilatation have little effect on hyperemic responses after occlusions of <10 seconds but may appropriately modify responses after release of occlusions lasting >30 seconds. These results pose problems for the adenosine hypothesis.

A different problem from the adenosine hypothesis stems from the recent work of Downey et al.[32] They showed that regional myocardial hypoxia produced by perfusion with blood of low oxygen partial pressure produced coronary vasodilatation of a degree similar to that induced by ischemic hypoxia, and that although ischemic myocardial hypoxia increased tissue concentrations of adenosine, nonischemic myocardial hypoxia reduced them. These findings run counter to previous observations that showed an increase in adenosine re-

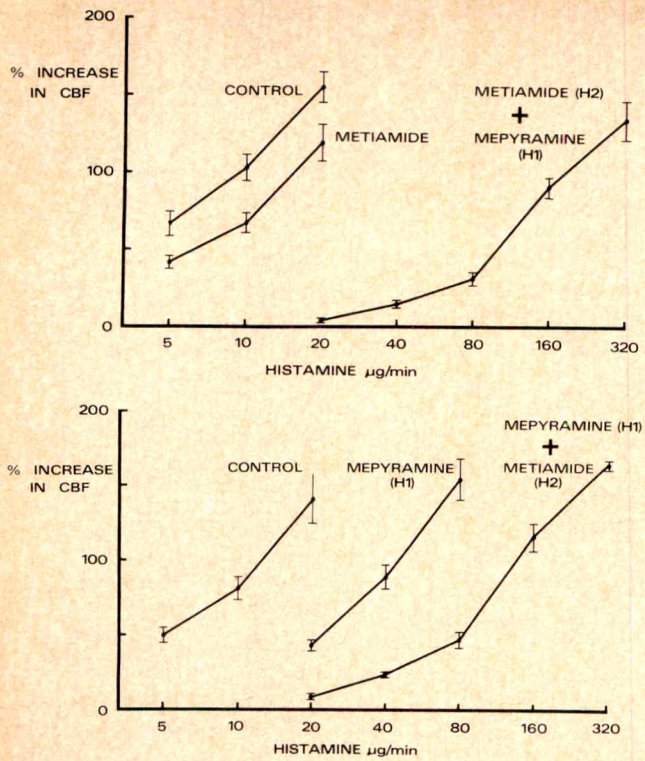

FIGURE 4. Top, dose-response curves determined by close-circumflex coronary artery histamine infusions in anesthetized dogs before and after blockade of the H_2 receptor with metiamide (100 μg/min) and the H_1 receptor with mepyramine (100 μg/min). Heart rate and blood pressure were unchanged (see text). CBF = coronary blood flow. Values are mean ± standard error. Reproduced from Giles et al[39] with permission of the publisher. **Bottom,** as in A except that the H_1 receptor was blocked first with mepyramine (100 μg/min) and then metiamide (100 μg/min) given so that both H_1 and H_2 receptors were blocked. Values are mean ± standard error. Both mepyramine and metiamide antagonize histamine-induced coronary vasodilatation, and the combination of the 2 shift the dose-response curve further to the right than either alone. Vasodilation is attenuated more by mepyramine, suggesting that H_1 receptors predominate. Reproduced from Giles et al[39] with permission of the publisher.

lease with any intervention creating an increased myocardial oxygen requirement, including hypoxia, and a good correlation between this increase and elevation in coronary flow.[9,19,24]

Such studies are critically dependent upon the delay between obtaining tissue and freezing it, but if the findings of Downey et al[32] are confirmed, they would constitute powerful evidence for the importance of oxygen or vasodilator metabolites other than adenosine or both contributing to coronary vasodilatation associated with nonischemic hypoxia.

Other Possible Vasodilator Mediators

It is beyond the scope of this review to consider other vasodilator mediators in detail. The effects of prostaglandins and the local release of neurotransmitters in neurally mediated changes are considered elsewhere in this symposium. Parratt[19] reviewed the evidence for contributions from carbon dioxide and locally released potassium; the results of recent work make it likely that these act as vasodilator mediators under certain circumstances without fully accounting for responses. Potassium release, for example, occurs after a 15-second coronary artery occlusion, but the time course of the release and the return toward normal is not the same as that of the hyperemic response.[33] Forrester[34] has discussed the evidence for a role for adenosine triphosphate.[34] It is a more powerful vasodilator than adenosine, and this action is unaffected by aminophylline.[35] There is, however, a fundamental problem of membrane permeability with adenosine triphosphate, in that leakage from myocardial cells probably only occurs with membrane damage. Under these conditions, it must have important local vasodilator effects.

Histamine is of special interest because it is present in high concentration in the human heart and is a powerful vasoactive agent. It may have a regulatory role in adrenergic neurotransmission,[36] but as yet no role for it in coronary flow regulation has been defined. Its cardiovascular actions have been extensively reviewed recently.[37] Histamine is a powerful dilator of small resistance vessels in the dog heart and human peripheral circulation, but constricts isolated large conducting coronary arteries in humans.[38] The involvement of H_1 and H_2 receptors in the dilatation of coronary resistance vessels in the dog is shown in experiments summarized in Figure 4, in which close-circumflex coronary artery infusions of histamine were given before and after H_1,H_2 and combined H_1- and H_2-receptor blockade. The dose-related increases in coronary blood flow that occurred without change in heart rate or blood pressure were attenuated more by H_1- than H_2-receptor blockade, but the effect of each potentiated the effect of the other. We could find no evidence in these studies for an involvement of histamine in postocclusion hyperemia in that this response was unaffected by combined H_1- and H_2-receptor blockade, which markedly attenuated histamine-induced flow increases of the same magnitude as those produced during reactive hyperemia.[39] But the same could be said for adenosine in similar experiments with aminophylline blockade.[35]

Myogenic Factors in Local Flow Regulation

The myogenic hypothesis and the idea of autoregulation of blood flow—that is, the maintenance of a relatively constant blood flow, over a wide range of perfusing pressures, to tissues whose myocardial oxygen demand remains unchanged—stems from the work of Bayliss.[40] The myogenic hypothesis suggests that elevation of vascular transmural pressure stretches arteriolar smooth muscle cells, inducing lengthened myofibrils to contract more forcefully, and that the ensuing vasoconstriction keeps contained a potential increase in blood flow. Lowering vascular transmural pressure does the reverse by reducing the forces tending to elongate circularly arranged vascular smooth muscle.

The myogenic response has been reviewed recently relative to the circulation as a whole[41] and the coronary circulation specifically.[42] These reviews summarize the powerful evidence for the existence of myogenic effects in the renal, limb, splanchnic and cerebral circulation, although direct proof is lacking in the latter. In the

coronary circulation, however, the evidence in inferential and studies have been hampered by the difficulty of separating metabolic from possible myogenic effects during autoregulation and myocardial reactive hyperemia. The latter has been extensively studied because it is a highly reproducible response in which metabolic and transmural pressure changes occur, and the magnitude of the response is not explicable in terms of metabolic mechanisms alone.[43] Studies from this laboratory in which 1 or 2 cardiac cycle coronary artery occlusions were performed in conscious and anesthetized dogs resulted in marked reactive hyperemia responses even though these would not, according to current knowledge, lower intracellular myocardial oxygen partial pressure.[44] Similar responses to single cycle occlusions have lately been shown to occur also in man.[45] Nevertheless the finding of significant variations in myocardial adenosine throughout individual cardiac cycles makes it theoretically possible for adenosine to be the mediator.[22] However, these responses to short occlusions cannot be attenuated by aminophylline nor can this discrepancy be explained by enhanced adenosine-induced vasodilator activity in the presence of reduced oxygen partial pressure and increased hydrogen ion concentrations, as suggested by Merrill et al[46]; subsequent experiments by the same group exclude that possibility.[47]

Two recent findings may further clarify the mechanisms of myocardial reactive hyperemia. Hintze and Vatner[48] showed in conscious dogs that large coronary arteries respond to release of 20-second coronary artery occlusions with delayed dilatation. In their experiments, this reached a maximum of 62 ± 4 seconds after release, when arterial cross-sectional area was 32 ± 9% above the control level; at this time, coronary flow had returned to preocclusion values.

These data are interesting in view of the reduced coronary vascular activity that occurs after a reactive hyperemic response and lasts for several minutes.[49,50] Taken together, these findings may provide an explanation for the dependency of myocardial reactive hyperemia on coronary artery pressure found by Dole et al,[51] consistent with a transient depression of the normal vascular reactivity to postocclusion pressure. As Dole et al suggest, a passive component to reactive hyperemia could account for the consistent postrelease overpayment of the flow debt in the heart.

The most recent finding is that the slow-channel calcium blockers nifedipine and verapamil markedly attenuate reactive hyperemic responses after release of short coronary artery occlusions (up to 30 seconds), when given in amounts that do not alter myocardial oxygen consumption, and that this is associated with a variable blockade of vasodilator responses to infused adenosine.[52] Diltiazem also reduces postocclusion hyperemia (10-second occlusions) but appears less effective.[53] These recent observations all suggest that alterations in intrinsic vascular smooth muscle function during and after the reactive hyperemic response do occur and cannot be explained entirely in terms either of metabolic or myogenic mechanisms as they are understood.

Belloni[24] emphasized the distinctions that should be drawn between the functional hyperemia resulting from increased myocardial activity, postocclusion hyperemia after release of a coronary artery occlusion, hyperemia associated with systemic hypoxia, and the hyperemia accompanying a decrease in perfusion pressure over the autoregulatory range. It is unlikely that these widely differing responses can be explained in terms of a single vasodilator mechanism; the involvement of several mechanisms, or combinations of mechanisms, is much more likely.

Coronary Anatomy and Blood Flow

Changes in vascular smooth muscle function alter flow within limits dictated by coronary anatomy. The latter must influence the distribution of flow. The anatomy of the coronary circulation and the extent of its collateral supply varies greatly between species; for example, there is a profuse collateral circulation in the dog not present in the pig, whose coronary anatomy closely resembles that of humans.[54] In humans, the size of named coronary arteries and the disposition of dominance between right and left coronary vascular systems vary greatly from person to person. The differences are presumably genetically determined. Two of my patients, 40-year-old monozygotic twins investigated for coronary artery disease, are of considerable interest in this regard in that each had identical coronary anatomy in terms of size of major arteries and the extent of the myocardium each supplied (Wilcken DEL, unpublished data).

Occlusions of a major coronary artery produce left ventricular impairment widely differing in extent and severity in different patients. This is evident from studies of patients with total left anterior descending artery obstruction as their only coronary artery lesion.[55] Whether the obstruction is proximal or distal is obviously important; for example, Brooks et al[55] found, not surprisingly, that patients with proximal obstructions were more likely to have a greater reduction in left ventricular function than those whose obstructions were distal to the first septal perforator branch. The major determinant of the variability is the amount of myocardium supplied by the obstructed artery, collaterals notwithstanding.[56] Because the area supplied by any individual artery varies from patient to patient, local, genetically determined, anatomic factors must be important in the pathophysiologic features of the coronary circulation. This fact, perhaps self-evident, is poorly appreciated.

General Conclusions

The concept of a transmural series of vascular waterfalls due to a gradient of compressing diastolic tissue pressures from the epicardium to the endocardium awaits confirmation. It has broad implications in relation to subendocardial ischemia and to the effect of hypertrophy on regional blood flow. Although present data show a significant role for adenosine in coronary blood flow regulation to be likely, it is also unlikely that adenosine is the sole mediator. Indeed, considering the importance of metabolic vasodilatation for norma

cardiac function, a unitary theory of regulation with a single vasodilator mediator would seem to lack built-in safety factors. As Parratt[19] has pointed out, it is unlikely that there is any 1 sole mediator of every kind of physiologic coronary vasodilatation. Evidence is accumulating for interrelations between naturally occurring coronary vasodilators in mediating flow responses, with important links provided by prostaglandins. The recent demonstration of reduced coronary blood flow in man after prostaglandin synthetase blockade with indomethacin is important evidence favoring a role for prostaglandins in human coronary flow regulation.[57] There is also evidence for the importance of intrinsic changes in vascular smooth muscle in postocclusion hyperemia and for the significance of anatomic variability in the coronary arteries in relation to myocardial damage in pathophysiologic states.

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Alpha-Adrenergic Regulation of the Coronary Circulation in the Conscious Dog

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To examine the role of neural and humoral factors in the control of coronary vasoactivity in conscious animals in which the complicating effects of general anesthesia and recent surgery were absent, dogs were instrumented with miniature pressure gauges in the aorta and left ventricle to measure aortic and left ventricular pressures and with flow probes in the left circumflex coronary artery to measure coronary blood flow. Several weeks after recovery from operation, experiments were conducted in the conscious dogs. Stimulation of the carotid chemoreceptor reflex elicted a biphasic response; initially striking reflex coronary vasodilation was observed: Coronary blood flow tripled even after changes in metabolic factors were minimized by pretreatment with propranolol. The chemoreceptor reflex coronary vasodilation was mediated both by cholinergic activation and withdrawal of alpha-adrenergic tone. The second phase of the response involved an increase in coronary vascular resistance, associated with elevated arterial pressure and an absolute reduction in coronary blood flow and coronary sinus oxygen content. The later period of coronary vasoconstriction was abolished by alpha-adrenergic blockade. Intravenous infusion of the alpha-adrenergic agonist methoxamine increased mean arterial pressure by 65 ± 5% and total coronary vascular resistance by 92 ± 14%. To determine whether the large coronary arteries were also under autonomic control, the dogs were instrumented with a pair of ultrasonic crystals on opposing surfaces of the left circumflex coronary artery to measure its diameter directly and continuously. Methoxamine reduced coronary cross-sectional area substantially, thereby constricting large coronary arteries and resistance coronary vessels. Thus, while the coronary arteries are regulated by changes in myocardial metabolic demands, they are also responsive to changes in neural stimuli. The most striking changes were observed with augmentation and withdrawal of alpha-adrenergic constrictor tone, which appear to be important in the control of large as well as small coronary vessels.

Until recently, neural control of the coronary circulation was considered a trivial component in the multifactorial control of coronary blood flow and vascular resistance. The current interest in coronary vasospasm, increased interest in the autonomic control of the coronary circulation and studies in experimental animals and in humans have corroborated its importance.

This review will not present all evidence for autonomic coronary vascular regulation, but will highlight the studies demonstrating the best examples of autonomic modulation of large and small coronary vessels. The studies described have been conducted in chronically instrumented, conscious animals. The advantages of this technique include the ability to measure variables in the coronary circulation and left ventricular function instantaneously and continuously and the absence of the complicating influences of anesthesia and recent surgery.[1]

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Methods

Mongrel dogs were anesthetized with pentobarbital sodium 30 mg/kg. All transducers were implanted through a thoracotomy in the fifth left intercostal space. To measure coronary blood flow, an electromagnetic or Doppler flow transducer was implanted in the left circumflex coronary artery. In dogs in which an electromagnetic flowmeter was used, a hydraulic occluder was implanted distally to confirm zero blood flow. Pacing electrodes were implanted on the right atrium. To measure left ventricular (LV) pressure and the first derivative of LV pressure (LV dP/dt), miniature pressure gauges (Konigsberg Instruments) were implanted in the left ventricle. Miniature pressure gauges were also implanted in the descending thoracic aorta. Heparin-filled Tygon™ (Norton)

catheters were implanted in the left atrium and descending thoracic aorta. To measure coronary diameter, 2 miniature 7-MHz ultrasonic transducers were implanted on opposing surfaces of the left circumflex coronary artery 3 to 6 cm from its origin. The ultrasonic transducers were covered with Insl-X® (Insl-X Products) and attached to a Dacron® (Dupont) backing. The Dacron was sutured to the outer adventitia of the coronary artery using Ethicon 5-0 suture. To measure right coronary artery blood flow and right ventricular pressure, a Doppler flow transducer was implanted in the right coronary artery and a miniature pressure gauge was implanted in the right ventricle through a right thoracotomy. During a subsequent operation using pentobarbital sodium, 30 mg/kg, and a right thoracotomy approach, a Tygon catheter was implanted in the coronary sinus in 5 dogs. In dogs in which carotid chemoreceptor reflex stimulation (CCRS) was to be carried out, a Tygon catheter was implanted in the common carotid artery just proximal to the carotid body using anesthesia with 10 mg/kg of sodium thiamylal.

LV and aortic pressures were measured with the implanted miniature gauges, which were calculated in vitro with a mercury manometer and cross-calibrated in vivo with pressure measurements from the aortic and left atrial catheters. Coronary blood flow was measured using a Benton square-wave electromagnetic flowmeter or a Doppler ultrasonic flowmeter.[2] Phasic coronary arterial diameter was measured instantaneously and continuously with an improved ultrasonic dimension gauge.[3–5] The frequency response of the dimension gauge is flat to 100 Hz. The drift of the instrument is minimal (<0.01 mm in 6 hours). To further ensure data reliability, repeated calibration references were obtained regularly throughout the experiments and the received ultrasonic signal was monitored continuously on an oscilloscope. Major changes in alignment of the crystals were detected in the received signal and invalidated the experiment.

The experiments were conducted 1 to 3 weeks after operation in healthy, conscious dogs. Left circumflex coronary arterial diameter, arterial pressure, LV pressure, LV dP/dt, left atrial pressure, left circumflex coronary artery blood flow and heart rate were continuously measured during a control period and during interventions. The interventions were performed on different experimental days.

The data were recorded on a 14-channel magnetic tape recorder (Bell & Howell) and played back on 2 multichannel oscillographs (Gould-Brush). Mean pressures and coronary diameters and blood flows were measured using RC filters with 2-second time constants. LV dP/dt was derived by differentiating the LV pressure signal using a Philbrick operational amplifier (Teledyne Philbrick) connected as a differentiator and with a frequency response of 700 Hz. A triangular signal with a known slope (rate of change) was substituted for the pressure signal to calibrate the differentiator directly. Heart rate was measured continuously with a cardiotachometer triggered by the LV pressure pulse. While the external coronary diameter was measured continuously, the internal radius was calculated by determining at autopsy the thickness and mass of a coronary artery with known length from the point at which the piezoelectric crystals were located. Thus, wall volume could be calculated as the quotient of mass and density ($d = 1.06\ g/cm^3$). After the wall volume, the wall thickness value and external diameter were determined, and the internal coronary diameter and cross-sectional area, which reflect large coronary arterial responses, were calculated. Late diastolic coronary resistance, which reflects primarily small coronary vessel resistance, was calculated as the quotient of late diastolic arterial pressure and late diastolic coronary blood flow. The mean and standard deviation were calculated for all variables.

FIGURE 1. The instrumentation for measurement and transmission o aortic and left ventricular pressures and coronary blood flow during exercise was carried by each dog in a backpack. The signals were transmitted to a mobile recording until that consisted of a van carrying FM communication receivers, subcarrier discriminators, signal processing electronics and a multichannel tape recorder. (Reprinted, by permission, from Trans Assoc Am Physicians, in press, 1982.)

Protocols

Experimental protocols: *Response to carotid chemoreceptor reflex stimulation: spontaneous respiration:* Heart rate was held constant (ventricular pacing) by electrical stimulation from an external pacemaker in all experiments. After control measurements of all variables, CCRS was achieved by a bolus (1 ml total volume) injection of nicotine into the catheter chronically implanted in 1 of the main carotid arteries. Increasing doses of nicotine (range from 1 to 10 μg) were administered to determine the dose of nicotine required to achieve peak coronary vascular effects in each dog. This dose was used throughout the remainder of the study. Triplicate responses of the measured variables to CCRS (which in the conscious, spontaneously respiring dog also elicits the pulmonary inflation reflex) were then determined. The cardiovascular effects elicited by the intracarotid injection of nicotine in this dose range are entirely reflex in nature in that the nicotine-induced effects are abolished by ipsilateral carotid sinus nerve section.[6–10] The integrated coronary vascular response to combined carotid chemoreceptor and pulmonary inflation reflex activation was further assessed after the sequential intravenous administration of the beta-adrenergic antagonist propranolol hydrochloride (1.0 mg/kg), the cholinergic antagonists atropine sulfate or atropine methyl bromide (0.1 mg/kg) and the alpha-adrenergic antagonist phentolamine (2.0 mg/kg). The adequacy of beta-adrenergic blockade was tested with isoproterenol (1.0 μg/kg, intravenously), that of cholinergic blockade with acetylcholine (40 μg/kg, intravenously), and that of alpha-adrenergic blockade with norepinephrine (1.0 μg/kg, intravenously).

Response to carotid chemoreceptor stimulation: controlled respiration: To avoid the confounding influences of changes in intrathoracic pressure and arterial blood gases associated with pulmonary inflation reflex activation, the effects of intracarotid nicotine were assessed on a separate day when ventilation was controlled by a respirator during succinylcholine chloride infusion (0.1 mg/kg/min, intravenously).

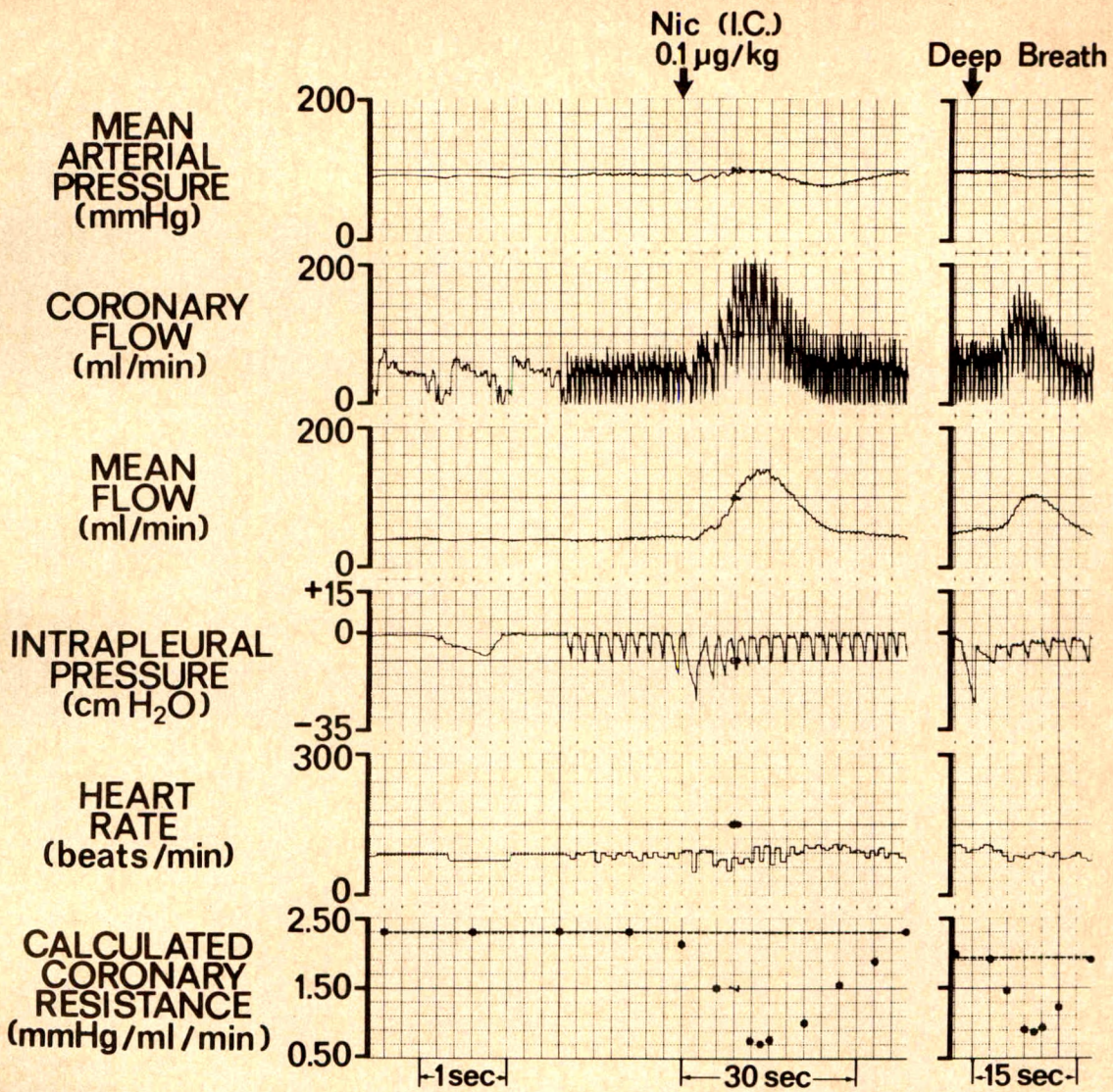

FIGURE 2. Effects of intracarotid (I.C.) administration of nicotine (NIC) in a conscious dog with spontaneous rhythm (**left section**) on mean arterial blood pressure, phasic and mean coronary blood flows, intrapleural pressure, heart rate and calculated coronary resistance. Intracarotid administration of nicotine elicited a striking increase in coronary flow and a reduction in coronary resistance immediately after an increase in the depth of respiration (indicated by the change in intrapleural pressure). The effects of a spontaneous deep breath in the same conscious dog are shown in the **second section.** The effects of the same dose (**third section**) and a much larger dose of intracarotid nicotine (**fourth section**) in the same dog are also shown after general anesthesia was induced with sodium pentobarbital. A spontaneous deep breath elicited a period of coronary dilation similar to that which occurred with intracarotid nicotine in the conscious state, but nicotine administered in the anesthetized dog did not evoke a substantial change in either respiration or coronary vasodilation. Reproduced from Circ Res 1975;37:664–673 with permission of the publisher.

Before these experiments, this protocol was reviewed by the Animal Care Committee of the institution and was found to conform to the guidelines for research in experimental animals. All dogs were lightly anesthetized with a short-acting barbiturate (thiamylal sodium, 2.0 mg/kg, intravenously) before intubation and succinylcholine administration. The larynx was sprayed with a topical anesthetic (Cetacaine®, Cetylite Industries) and the endotracheal tube was coated with a lidocaine paste. Because these dogs were only lightly tranquilized, no intervention was performed that would not be fully tolerated by the conscious dog in the absence of succinylcholine. At the end of each experiment, the dogs were given an intramuscular injection of morphine sulfate (10 mg) as an analgesic.

The right and left coronary response to selective CCRS, as well as changes in arterial and coronary sinus blood gases and oxygen contents, were first assessed with the autonomic nervous system intact and then after the sequential intravenous administration (doses noted above) of propranolol, atropine and phentolamine.

Responses to free ranging exercise: During the exercise periods, instrumentation necessary for the continuous transmission of aortic pressure, LV pressure and left circumflex coronary blood flow signals by radiotelemetry (described later) was carried by each dog in a backpack. The exercise regimen consisted of each dog running freely behind a mobile recording van over a hilly half-mile course (Fig. 1) in the absence of pharmacologic blocking agent (unblocked condition), or 3 to 5 minutes after the intravenous administration of a beta-receptor blocker (propranolol hydrochloride 1 mg/kg), an alpha-receptor blocker (phentolamine, 1 to 2 mg/kg) or after combined beta and alpha blockades. Heart rate was held constant during exercise by electrical pacing. The entire exercise protocol for each dog usually was com-

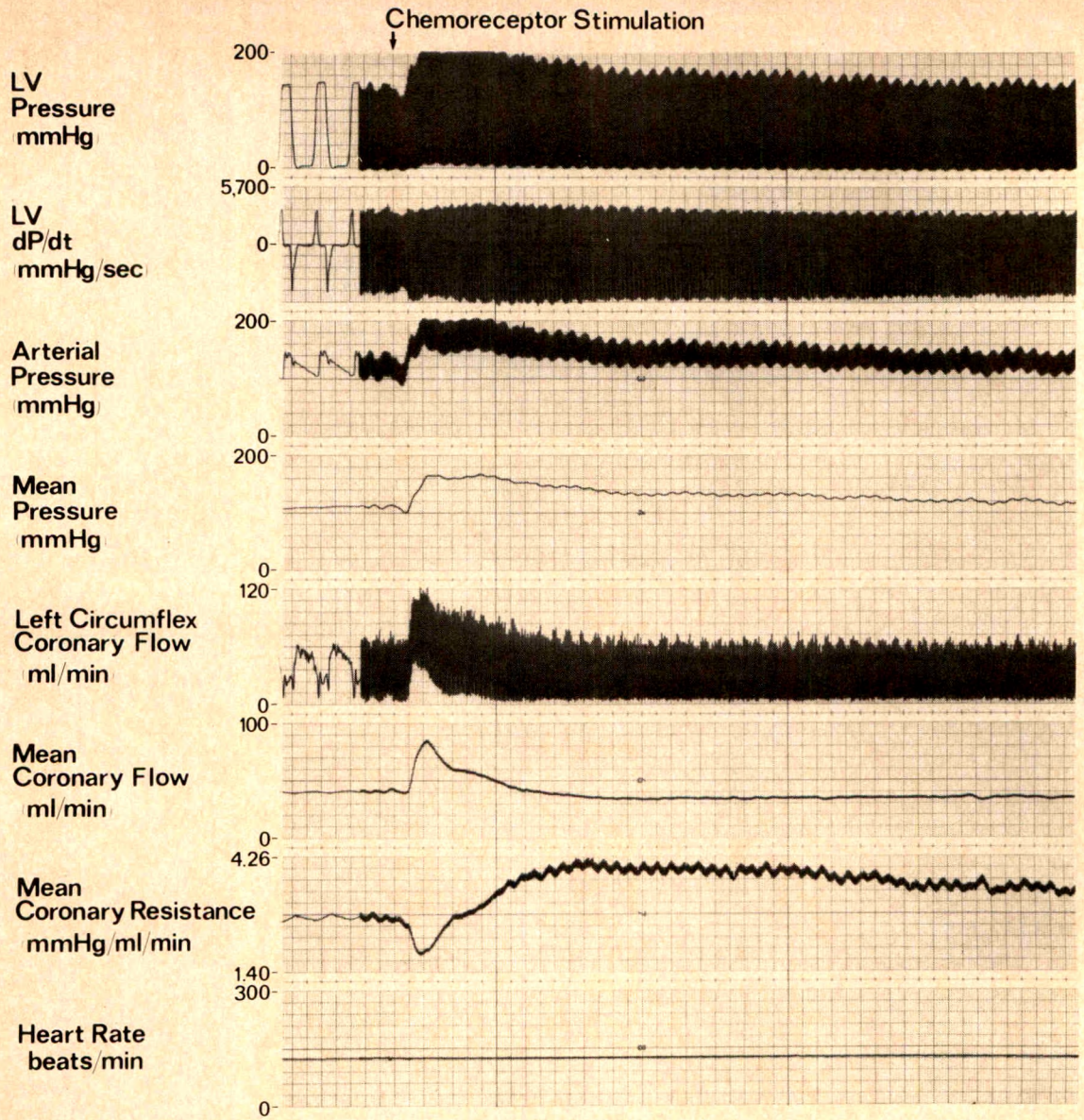

FIGURE 3. Effects of intracarotid administration of nicotine in a conscious dog with controlled ventilation of left ventricular (LV) pressure, LV dP/dt phasic and mean arterial pressure and left circumflex coronary blood flow, calculated mean coronary resistance and heart rate. Chemorecepto stimulation elicited an initial striking increase in coronary flow and a reduction in coronary vascular resistance. This was followed by a period o coronary vasocontriction characterized by a reduction in coronary blood flow in the face of a sustained increase in arterial pressure. This perio of vasoconstriction was also characterized by a decrease in coronary sinus oxygen content and could be eliminated by prior alpha-adrenergic recepto blockade.

pleted over a 1-week period, with a maximum of 2 exercise periods per day. Three- to 5-hour rest intervals were allowed between exercise periods on a given day. The order of the exercise regimen was randomized to avoid the potentially confounding influences of dog training or altered sensitivity to the adrenergic antagonists that may accompany multiple exercise periods. Moreover, duplicate exercise runs were performed in selected dogs to assess the consistency of the responses of the measured variables during exercise.

System for telemetry of data: Continuous measurements of left circumflex coronary blood flow, heart rate, aortic pressure and LV pressure were radiotelemetered while the dogs were standing quietly at rest or running freely in the field behind a mobile recording van (Fig. 1). Speeds of 25 to 35 mph were achieved routinely by these dogs in the absence of any blocking agent. Whereas running speeds were generally slowe in the presence of the adrenergic antagonists (10 to 20 mph) in all cases the severity of the exercise period (as reflected by the time required to traverse the exercise course) afte blockade of alpha-receptor activity was either less than o equal to the level of exercise with alpha-receptor activity in tact. Descriptions of the instrumentation and techniques use to transmit continuously the left circumflex coronary bloo flow, aortic pressure and LV pressure signals by radiotelem etry have been reported in detail.[3,11] Briefly, the signals fron the aortic and LV pressure implant system were transmitte from the dogs to the remote recording unit by way of a FM/FM subcarrier telemetry system. The Doppler ultrasoni flowmeter signal was frequency modulated on the carrie frequency and did not require an additional subcarrier. Th

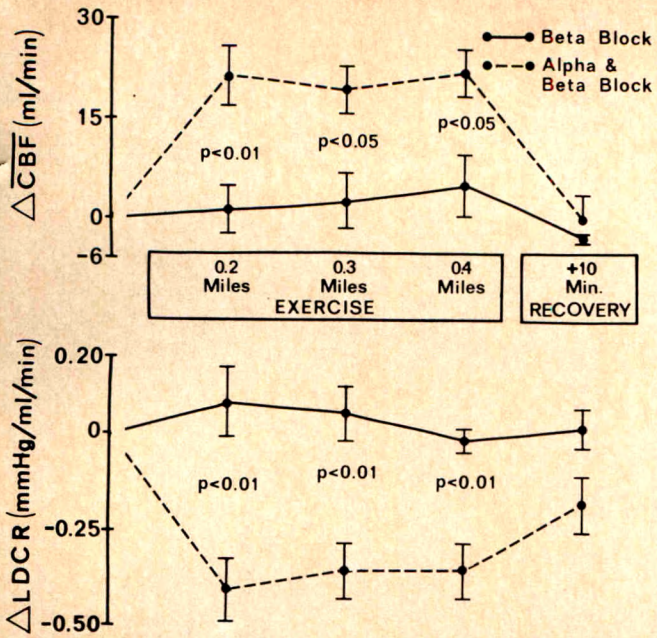

FIGURE 4. Average (± standard error of the mean [SEM]) changes in mean left circumflex coronary blood flow (ΔCBF) and late diastolic coronary resistance (ΔLDCR) of 9 dogs during spontaneous exercise at 0.2, 0.3 and 0.4 miles and 10 minutes after cessation of exercise after pretreatment with propranolol with alpha-receptor activity intact (beta block) and after blockade of alpha-receptor activity (alpha and beta block). Heart rate was held constant at approximately 190 beats/min by electrical pacing. Reproduced from Circ Res 1979; 45: 654–600 with permission of the publisher.

mobile recording unit consisted of a van carrying FM communication receivers, subcarrier discriminators, signal processing electronics, and a multichannel tape recorder (Honeywell model 5600-C). A commercial whip antenna mounted on the roof of the van received the signals transmitted from the dog. Power for the equipment was obtained from two direct-current (DC) to alternating-current (AC) inverters (Heathkit model MP-14 and Wilmore model 1057-12). Each of these units was powered by one 12-V battery. The FM tuners (Heathkit model AJ-15) were modified to disable the FM deemphasis network and multiplex circuitry, providing video response sufficient to recover the modulated subcarrier signals. The output of the FM tuners was applied directly to the input of the 2 subcarrier frequency discriminators (Airpax model FDS-30). These discriminators converted the frequency modulation signals to DC voltages proportional to the signals measured in the dog. These DC voltages then were applied to FM channels of the instrumentation tape recorder. During the experiment, commentary was recorded on a voice channel of the tape recorder.

Results and Discussion

Alpha-adrenergically mediated coronary vasodilation: Activation of the carotid chemoreceptor and pulmonary inflation reflexes provides the most striking example of alpha-adrenergically mediated coronary vasodilation. In the conscious dogs breathing spontaneously, injections of minute quantities of either nicotine or cyanide into the common carotid artery just proximal to the carotid body elicits a marked increase in ventilation, which is rapidly followed by striking (2- to 3-fold) increases in coronary blood flow. This increase in coronary blood flow occurs in the face of little change in arterial pressure (Fig. 2), no change in heart rate or with heart rate held constant, and before any significant alterations in LV wall tension and myocardial contractility. Furthermore, the increase in coronary blood flow is accompanied by an increase in coronary sinus oxygen content and reduction in the arteriovenous oxygen difference. Thus, the dilation is clearly not mediated by metabolic mechanisms.

To confirm that the afferent pathway was neural, experiments were conducted after section of the ipsilateral carotid sinus nerve. Under these conditions, absolutely no effect was observed after intracarotid injection of either nicotine or cyanide. To confirm that the efferent pathway was neurally mediated, the experiments were conducted in the presence and absence of selective and combined autonomic blockade. Since the peak coronary vasodilation after CCRS preceded inotropic changes, it could be predicted that beta-adrenergic blockade would not modify the coronary vasodilation due to CCRS. Indeed, that is what was observed. Atropine, 0.1 mg/kg, increased cardiac rate, and consequently partially dilated the coronary bed on a metabolic basis. However, CCRS in the presence of cholinergic blockade still induced significant vasodilation, attaining peak levels similar to those in the absence of cholinergic blockade. The addition of phentolamine almost abolished the coronary vasodilation in response to CCRS.

Thus, CCRS in the conscious dog elicits striking coronary vasodilation. The efferent mechanism of this vasodilation appears to involve withdrawal of alpha-adrenergic tone, since it is blocked by phentolamine.

It is important to keep in mind that these experiments were carried out in conscious dogs respiring spontaneously. The CCRS-induced coronary vasodilation was always preceded by an increase in depth of respiration. The afferent mechanism responsible for the vasodilation may well be the pulmonary inflation reflex and not the carotid chemoreceptor reflex. A similar coronary vasodilator response can be evoked by increasing the depth of ventilation either spontaneously (deep breath) or mechanically (increasing the volume of a respirator).[6] These responses are eliminated by alpha-adrenergic receptor blockade or attenuated markedly by vagotomy.[6] In contrast, carotid chemoreceptor reflex–induced coronary vasodilation can be blocked by atropine.[6,12]

Alpha-adrenergic receptor coronary vasoconstriction: Most evidence for alpha-adrenergically mediated vasoconstriction is derived from experiments in which coronary driving pressure increases and coronary blood flow remains constant, thereby eliciting an increase in calculated coronary vascular resistance.[13–18] These increases in calculated coronary vascular resistance can be eliminated by alpha-adrenergic receptor blockade.[13–18]

Recently, we observed an example of coronary vasoconstriction that is characterized by an increase in coronary driving pressure and absolute reduction in coronary blood flow.[10] This response occurs with CCRS,

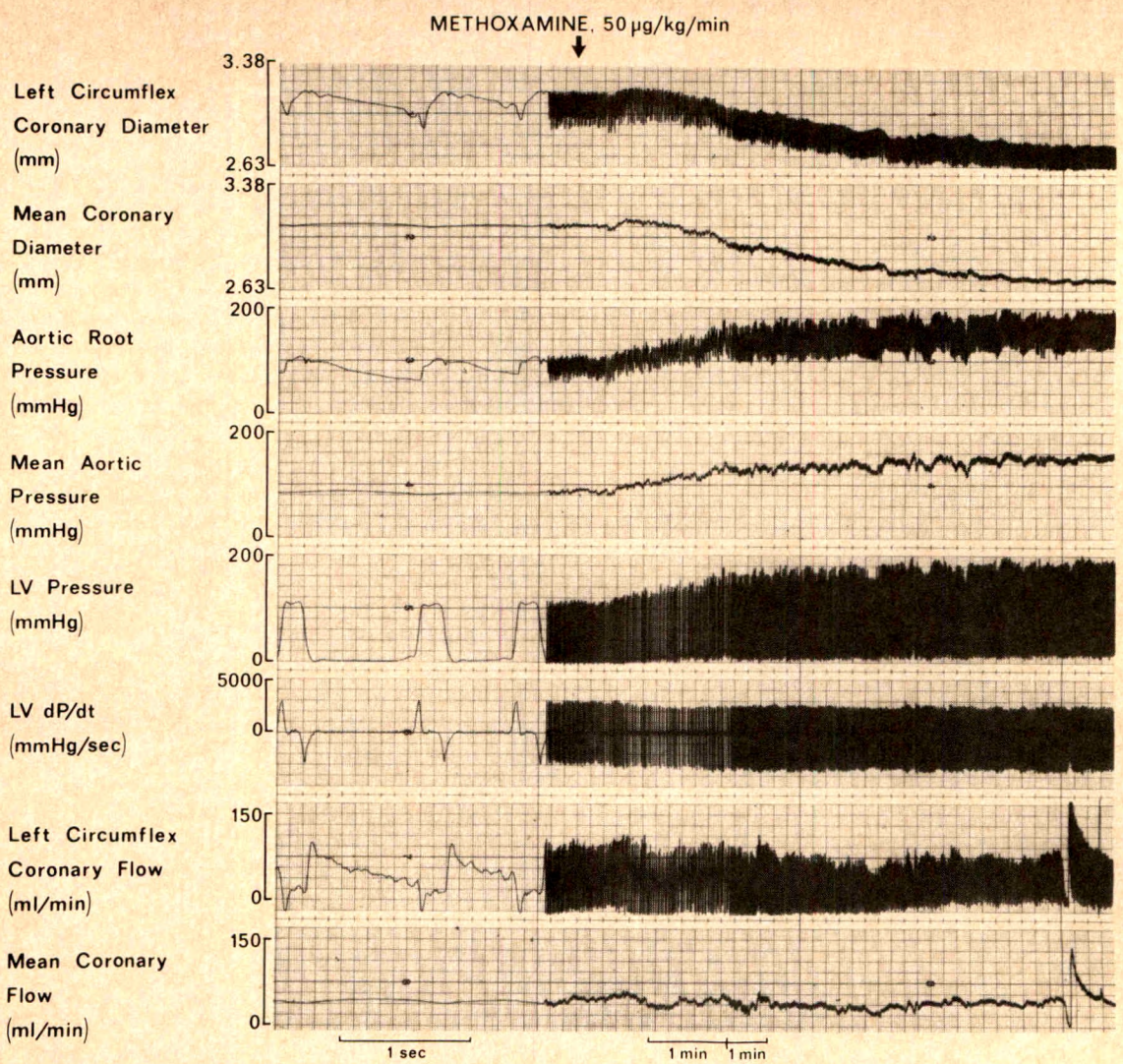

FIGURE 5. The effects of a 10-minute infusion of methoxamine, 50 μg/kg/min, in a conscious dog are depicted on simultaneous and continuous measurements of phasic and mean left circumflex coronary artery diameter, aortic root pressure, left ventricular (LV) pressure, LV dP/dt and phasic and mean left circumflex coronary blood flow. Methoxamine increased coronary diameters only initially and transiently and then induced striking sustained reductions in coronary diameters at a markedly increased aortic pressure. A mechanical zero for the blood flow recording is shown at the end of the experiment. The marked sinus arrhythmia is characteristic of the conscious dog. Reproduced from J Clin Invest 1980;65:5–14 with permission of the publisher.

but later, after the initial period of coronary vasodilation has subsided (Fig. 3). The late period of vasoconstriction is much more prominently displayed in the right coronary circulation than the left. This is probably because CCRS is accompanied by a moderate increase in afterload for the left, but not the right, ventricle. The right coronary artery supplies only the right ventricle in the dog and, thus, would not demonstrate an increase in blood flow due to enhanced myocardial metabolic demands faced by the left ventricle. The period of coronary vasoconstriction is associated with a decrease in coronary sinus oxygen content and a widening of arteriovenous oxygen difference across the heart. This later period of coronary vasoconstriction is not blocked by either beta-adrenergic or cholinergic blockade, but can be virtually eliminated by alpha-adrenergic blockade.

The afferent mechanism of this late period of coronary vasoconstriction is most likely the carotid chemoreceptor reflex, since the response is even more intense in the presence of controlled ventilation,[10] that is, where the complicating influences of the pulmonary inflation reflexes are absent. Moreover, under these conditions atropine eliminates the early vasodilation but leaves intact the later period of vasoconstriction. Therefore, the later vasoconstrictor response is not necessarily linked to the early vasodilator response.

These experiments demonstrate that stimulation of reflex adrenergic neural pathways is powerful enough to reduce coronary blood flow and coronary sinus oxygen content despite an elevation of coronary driving pressure in the conscious animal.

Alpha-adrenergic coronary vasoconstriction during exercise: Severe exercise is associated with intense sympathetic drive to the heart. This intense sympathetic drive may also affect the coronary vessels during severe exercise. To test this hypothesis, we ex-

amined responses to near-maximal exercise in dogs in the presence and absence of alpha-adrenergic receptor blockade. In the presence of alpha-adrenergic receptor blockade, coronary vascular resistance decreased to a significantly lower level than in the absence of alpha-adrenergic receptor blockade.[11] These experiments could be criticized on the basis that heart rate and myocardial contractility were uncontrolled. To obviate these criticisms, exercise was studied with heart rate held constant and after pretreatment with beta-adrenergic receptor blockade, but in the presence and absence of alpha-adrenergic blockade. Again, exercise of similar intensity elicited significantly greater coronary vasodilation in the presence compared with the absence of alpha-adrenergic receptor blockade[11] (Fig. 4). Subsequent studies by Gwirtz and Stone[19] and Heyndrickx et al[20] also demonstrated a component of alpha-adrenergic coronary vasoconstriction during exercise, which was associated with a widening of arteriovenous oxygen difference across the heart. All of these studies suggest that alpha-adrenergically mediated vasoconstriction attenuates the metabolic vasodilation associated with exercise.

Alpha-adrenergic vasoconstriction of large coronary arteries: Until recently, all evidence for large coronary arterial vasoconstriction was indirect. We developed techniques to measure large coronary arterial diameter in conscious animals.[5] To determine whether the large coronary arteries constricted in response to alpha-adrenergic stimulation, we examined responses of these large coronary arteries to an infusion of a potent alpha-adrenergic receptor agonist, methoxamine, 50 μg/kg/min.

Methoxamine elicited a marked increase in peripheral vasoconstriction accompanied by a substantial increase in arterial pressure. It was expected that coronary dimensions would increase passively in response to the elevated distending pressure induced by methoxamine infusion, and this is what was observed initially, but only transiently with methoxamine. However, with continued alpha-adrenergic receptor stimulation, coronary cross-sectional area rapidly returned to control levels and then decreased significantly below control for the remainder of the infusion period (Fig. 5). These data indicate that alpha-adrenergic receptor vasoconstriction of the large coronary arteries is powerful enough to oppose the tendency of arterial pressure to dilate these arteries. Moreover, the changes in vessel caliber cannot be ascribed to a reduction in metabolic requirements of the heart,[21] because heart rate was not significantly different from control, yet preload and afterload were both increased. Calculated total coronary vascular resistance increased 92% with methoxamine, suggesting that vasoconstriction occurred throughout the coronary bed; this is consistent with the results from a recent study in anesthetized dogs by Kelley and Feigl.[18]

These results indicate that in the conscious animal, large coronary vessels not only respond passively to changes in distending pressure, but also undergo substantial active changes in cross-sectional area. Alpha-adrenergic receptor activation reduces coronary cross-sectional area even in the face of marked increases in distending pressure.

Thus, the large and small coronary vessels of conscious dogs are regulated extensively by alpha-adrenergic mechanisms. Whether these mechanisms are of greater importance in the presence of coronary artery disease, and whether they could play a role in the pathogenesis of coronary vasospasm, remains to be determined.

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Prostanoids in Platelet-Vascular Interactions

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Prostacyclin, the labile prostanoid product of arachidonic acid metabolism in vascular endothelium, is the most potent known inhibitor of platelet aggregation and is highly effective in relaxing vascular smooth muscle. Its production is probably critically important in the maintenance of an intact vasculature. Although there is some evidence that prostacyclin circulates as a hormone, it is probably most important as a locally active agent in preventing thrombosis and maintaining patent vessels. Several factors can influence prostacyclin production, the most important of which probably act locally at sites of vessel wall injury. The mos promising therapeutic approaches toward usin prostacyclin's beneficial effects in vascular diseas may lie in the use of drugs aimed at increasin prostacyclin production. Among these are throm boxane synthesis inhibitors, which act by divertin prostaglandin endoperoxides through the prosta cyclin synthetase pathway, and lipoxygenase in hibitors, which might act chiefly by preventin formation of metabolites capable of inhibitin prostacyclin synthetase.

The discovery of thomboxane A_2 (TxA_2) as the most potent known promotor of platelet aggregation[1] focused attention on platelet arachidonic acid metabolites as major factors in the development of thrombi in blood vessels. Indeed, this provided the stimulus to the trials of antiplatelet drugs that began in the mid-1970s.[2] Their lack of conspicuous success suggests that thromboxane-mediated platelet aggregation is not the major contributor to coronary thrombus formation, and indicates that TxA_2 produced by platelets might not contribute substantially to coronary vasospasm and ischemia.[2]

The discovery of prostacyclin (PGI_2)[4] has altered fundamentally our understanding of these processes; this prostanoid may be a key factor in prevention of thrombosis and vasospasm by its actions as the most potent known inhibitor of platelet aggregation and as a potent vasodilator. PGI_2 was first recognized as a labile product of arachidonic acid metabolism, generated enzymatically by aortic microsomes from prostaglandi endoperoxides as substrate; it is an extremely poten inhibitor of platelet aggregation and is capable of re laxing vascular smooth muscle. From the very earlies experiments with this material, it appeared that PGI was an important factor in platelet-vessel wall inter actions.[5] For example, aortic microsomes added t platelet-rich plasma inhibited platelet aggregation,[6] a effect shown specifically to be a result of the generatio of PGI_2 from endoperoxides presumably supplied by th platelet. From this type of observation came the view that endothelial cells did indeed obtain their endo peroxides from platelets, and that generation of PGI by endothelial cells explained why platelets did no constantly aggregate when coming into contact wit vessel walls. The concept that endoperoxides from th platelets might be the sole substrate for endothelia PGI_2 synthesis has not been maintained, however, be cause it is clear that aortic and venous endothelial cell can produce PGI_2 in the absence of platelets.[8] Thus although under some circumstances platelet endo peroxides may contribute to endothelial PGI_2 forma tion, for the most part it seems likely that endothelia cells generate their own endoperoxides from arachidoni acid liberated from its esterified form in membran phospholipid.

Figure 1 illustrates the major pathways of cellula metabolism of arachidonic acid by way of the cycloox

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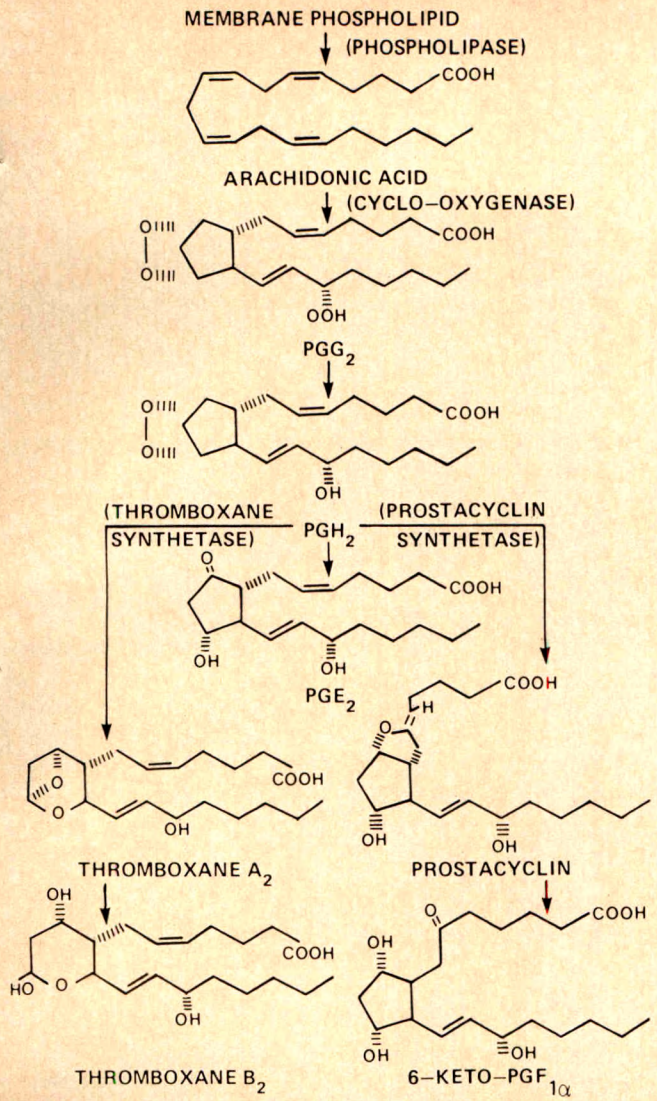

FIGURE 1. Pathways of metabolism of arachidonic acid via cyclooxygenase.

ygenase route. Control of the key enzymes in the pathways is crucial in determining the pattern of biologically active metabolites formed in individual tissues. These enzymes are regulated by levels of available substrates, the direct actions of other metabolites and of mediators such as cyclic nucleotides or calcium ions, or the indirect actions of external influences such as local or systemic hormones or vasoactive agents. Definition of the factors regulating PGI_2 production by endothelial cells is of considerable importance to our understanding of the mechanisms of thrombus formation and vascular spasm.

Actions of Prostacyclin and Thromboxane A_2

The actions of PGI_2 and TxA_2 that are relevant to their roles in cardiovascular physiology and disease are chiefly their opposing effects on blood platelets and vascular smooth muscle. TxA_2 is a potent inducer of platelet aggregation and secretion,[1] but the fact that prostaglandin endoperoxides themselves can probably induce platelet aggregation suggests that blockade of thromboxane production by platelets will not impair their ability to aggregate by mechanisms that involve arachidonic acid metabolism. The biochemical actions of thromboxane upon the platelet that are thought to mediate its aggregatory effect consist of an inhibition of platelet (cyclic AMP) production[9] and mobilization of calcium stores from within platelet granules. The antiaggregatory effect of PGI_2 requires for its initial action upon platelets the stimulation of adenylate cyclase.[10,11] Potentiation of the antiaggregatory action of PGI_2 by dipyridamole can be explained by inhibition of cyclic nucleotide phosphodiesterase activity.[12] The platelet process regulated by cyclic AMP probably include both inhibition of enzymatic liberation of arachidonate from platelet membranes, thus limiting formation of aggregatory endoperoxides and thromboxane, and inhibition of calcium release from platelet granules. The inhibition of aggregation by prostacyclin is achieved at much lower concentrations than those required to inhibit platelet adhesion,[13] allowing platelet involvement in vascular repair while preventing thrombus formation.

These opposing actions of PGI_2 and TxA_2, one favoring vascular patency and continuing blood flow and the other vascular constriction and thrombosis, were the basis of proposals[4,5,7] that a balance between production of the 2 was necessary for the maintenance of a healthy vasculature.

Prostacyclin and Thromboxane A_2 in Disease

Before PGI_2 was discovered and its importance realized, antithrombotic therapy was aimed at inhibiting TxA_2 production by using drugs to inhibit the cyclooxygenase enzyme. However, clinical effects were not striking; furthermore, prevention of TxA_2 production was associated with no more than a prolongation of bleeding time. Thus, the importance of TxA_2 as a major determinant in thrombotic states was questioned, particularly with increasing evidence of the production and action of PGI_2.

The view that PGI_2 production may be more important than TxA_2 production in determining spasm and ischemia is supported by recent clinical data. Thus, coronary sinus/aortic ratios of thromboxane B_2 (TxB_2) were found to be higher in patients with coronary artery disease and pain in the previous 24 hours than in those with more remote pain or without coronary artery disease.[14] On the other hand, in patients with vasotonic angina pectoris, the TxB_2 increase in coronary sinus blood associated with ischemia occurred well after the onset of ischemia.[15] Furthermore, indomethacin did not reduce the frequency or duration of angina. The likely interpretation of these observations may be that TxA_2 generation by platelets does not initiate large-vessel constriction. Thus, although increased amounts of TxB_2 have been found in peripheral blood[16] and coronary sinus blood[14] of patients with vasotonic angina, and in coronary sinus blood of patients with other forms of angina,[15] it is not possible to assess the extent of the contribution made by activated platelets. Alternatively, decreased PGI_2 production may be an important factor

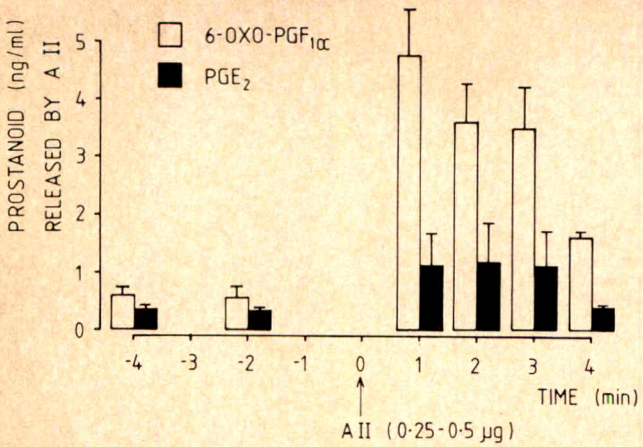

FIGURE 2. Effect of angiotensin II (AII) infusion into rat mesenteric vasculature upon release of prostaglandin E_2 (PGE_2) and 6-keto-$PGF_{1\alpha}$. Reproduced from Nolan et al[29] with permission of the publisher.

TABLE I Effect of Isoproterenol and Prostacyclin on Bovine Aortic Endothelial Cell Cyclic AMP

	Cyclic AMP/10^5 Cells (pmol)
Control	6.6 ± 0.5
Isoproterenol (10^{-7} *M*)	14.3 ± 0.4
Isoproterenol (10^{-6} *M*)	32.4 ± 1.1
Isoproterenol (10^{-5} *M*)	42.1 ± 1.2
Prostacyclin (10^{-7} *M*)	10.1 ± 0.3
Prostacyclin (10^{-6} *M*)	27.4 ± 0.4
Prostacyclin (10^{-5} *M*)	35.2 ± 0.6

Cellular cyclic AMP was assayed[10] after incubation of monolaye for 5 minutes in 1 m*M* of isobutylmethylxanthine.

TABLE II Effect of Elevation of Cyclic AMP on Endothelia Cell 6-keto-$PGF_{1\alpha}$ Production

	6-keto-$PGF_{1\alpha}$/10^6 Cells (ng)	
Control	2.4 ± 0.16	
Thrombin (2.5 U/ml)	10.3 ± 0.29	
Thrombin (2.5 U/ml) + isoprenaline (10^{-6} *M*)	7.4 ± 0.19	p <0.05
Thrombin (2.5 U/ml) + isoprenaline (10^{-6} *M*) + dipyridamole (10^{-5} *M*)	2.5 ± 0.21	p <0.001
Thrombin (2.5 U/ml) + dipyridamole	4.2 ± 0.24	p <0.001

Bovine aortic endothelial cells in monolayer culture were incubate for 30 minutes and media assayed for 6-keto-$PGF_{1\alpha}$.[29]

in the development of vasospasm. It has been thought likely that the major source of PGI_2 for maintenance of coronary vascular tone is the coronary vascular endothelium[17]; however, recent investigations suggest that pericardial fluid PGI_2, produced by the visceral and parietal pericardium, might contribute to the maintenance of coronary vascular tone, at least in the large, superficial coronary vessels.[18] Maintenance of normal PGI_2 production in or near vessels may be essential for the prevention of thrombosis and the regulation of vascular tone.

Experimental evidence in rabbits[19] and some data in man[20] indicate that atherosclerotic vessels have a reduced capacity to produce PGI_2, a phenomenon that could result from the effect of the lipid peroxides of atherosclerotic plaques that[21] inhibit PGI_2 production.[22] Disease states in man in which increased sensitivity to platelet-aggregating agents and increased production of TxA_2 by platelets are observed presumably result from a shift of endoperoxides toward thromboxane production; this may be the result primarily of prostacyclin deficiency. Such a mechanism may indeed operate in some forms of diabetic vascular disease. Aortas of diabetic rats produce less PGI_2 in vitro than do aortas of control rats; this deficiency can be prevented or corrected by insulin treatment.[23] Similar observations have been made by others in experimental diabetes[24]; furthermore, incubations of human diabetic vessels have provided results consistent with this finding.[25] Isolated glomeruli prepared from diabetic rats do not show the same deficient PGI_2 production as do large vessels,[26] suggesting that PGI_2 deficiency might be a feature of the large-vessel rather than of the small-vessel disease of diabetes. Indeed, the demonstration of certain differences between the behavior of endothelial cells of macrovascular and microvascular origin[27] indicates that we should not conclude that the processes controlling PGI_2 production are identical in the 2 types of vessel. It is important, therefore, to understand the mechanisms that regulate PGI_2 formation by endothelial cells of large and small vessels, and perhaps also by the pericardium if peri cardial PGI_2 contributes to maintenance of coronar vascular tone.

Regulation of Prostacyclin Production

The factors that can influence PGI_2 production ma be circulating or local. Angiotensin II increases PGI production upon infusion into rat mesenteric ves sels.[28,29] The peptide produces this effect by promotin release of arachidonic acid from membrane phospho lipid,[29] in a manner similar to the action of bradykinin.[3] In studying the action of angiotensin II in the isolate vasculature, we noted a selective increase in PGI_2 re lease (Fig. 2), suggesting either that mesenteric vascula endothelium is particularly rich in PGI_2 synthetase o that the enzyme is closely coupled to cyclooxygenase i those cells. If this action of angiotensin II is physiolog ically important, the peptide may act as a local rathe than as a circulating hormone. Certainly, bradykini and related substances are regarded as locally activ agents. Moreover, most of the other endogenous factor capable of stimulating PGI_2 production appear mor likely to act as local rather than as systemic effectors This applies to thrombin,[31] histamine[32] and platelet derived growth factor, the major protein constituent o the platelet that stimulates PGI_2 production.[33] Indeed local events may be more important than circulatin factors in the regulation of vascular PGI_2 production

Systemic hormonal regulation of PGI_2 productio would be easier to accept if it were firmly establishe that the prostanoid circulates as a hormone. This is however, an area of some dispute. There is biologic assay

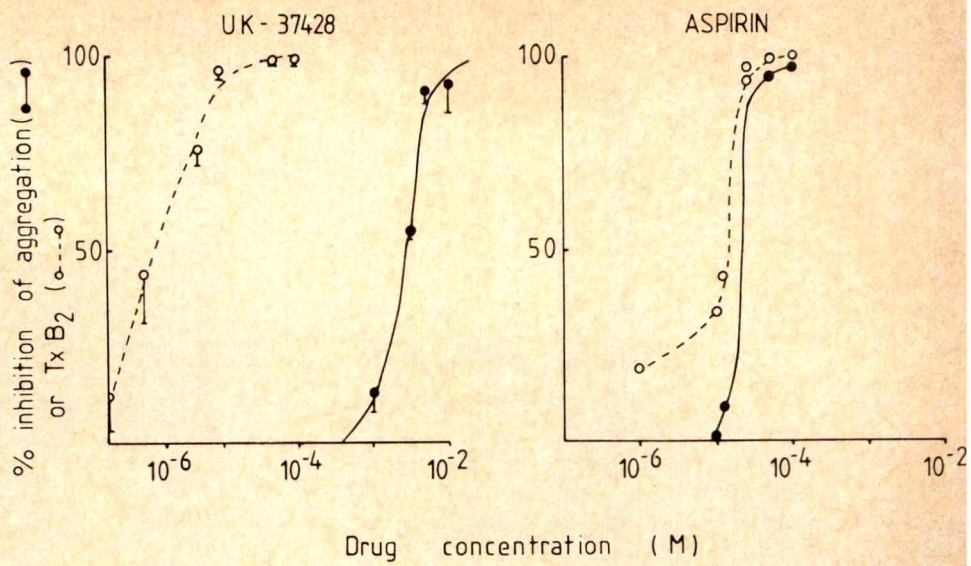

FIGURE 3. Effects of dazoxiben (UK-37,248) and aspirin on platelet aggregation and thromboxane B_2 (TxB_2) production. Each drug was incubated at the indicated concentrations with human platelet-rich plasma, and aggregation responses and TxB_2 production were measured after 5 minutes of incubation with 0.8 m*M* arachidonic acid. Results are expressed as percent inhibition of aggregation (**closed circles**) or of TxB_2 production (**open circles**). Methods used in these experiments have been published.[44] Dazoxiben (UK-37,248) was provided by Dr. H. A. M. Tyler, Pfizer Central Research, Sandwich, Kent, United Kingdom.

evidence that PGI_2 does circulate[35,36]; furthermore, whereas the lungs rapidly inactivate other prostanoids, they do not do so to PGI_2.[36] However, the conclusion that PGI_2 is a systemic hormone circulating in effective concentrations is seriously questioned by the data of Haslam and McClenaghan,[37] who used a very sensitive bioassay to show that fresh arterial blood from normal rabbits contains insufficient PGI_2 or 6-keto-$PGF_{1\alpha}$ to affect platelet function.

Among the local determinants of PGI_2 production are cyclic nucleotides and other products of arachidonate metabolism, amounts of any of which could be influenced by circulating factors. Thus, endothelial cell cyclic AMP is increased by isoproterenol and by PGI_2 itself[38–40] (Table I). The increase in cyclic AMP can inhibit phospholipase activity and regulate formation of PGI_2 within the endothelial cells[40] (Table II). This constitutes an autoregulatory system by which endothelial cell PGI_2 can regulate its own production. Furthermore, beta-adrenergic agonists can similarly modulate PGI_2 production. Although beta-adrenergic blocking drugs prevent this response directly,[40] whether they can influence PGI_2 production by vascular endothelium in vivo is not known.

The sensitivity of PGI_2 synthetase to inactivation by hydroperoxy-fatty acids[22,41,42] suggests that products of the lipoxygenase pathway of arachidonate metabolism play a regulatory role in the normal or pathologic production of PGI_2.

Undoubtedly, several other important control processes regulate PGI_2 formation, and various combinations of these operate during tissue damage. Thus, when vascular injury takes place, the local event of injury would result in stimulation of adjacent endothelial cells to produce PGI_2. The actual stimuli to PGI_2 production in such circumstances could be several, including thrombin and platelet-derived growth factor. Increased levels of PGI_2 might result from stimulation of enzymes directly in the pathway of arachidonate metabolism or from removal of inhibitory influences, such as lipoxygenase products. In atherosclerosis and diabetes, the disease process appears to result in a decreased PGI_2 production, thus favoring the formation of thrombi; under these circumstances, platelet-generated TxA_2 might contribute the development of vascular spasm.

Considering platelet-vessel wall interactions in this way, we see a system in which the tendency is toward thrombosis—a tendency overcome by the constant production of an antithrombotic vasodilator substance (PGI_2). At times of extra stress, for example, in vessel wall injury, this substance is produced in increased amounts; in certain disease states, decreased PGI_2 production favors thrombus formation.

Alteration of Prostacyclin Production by Drugs

With the knowledge of PGI_2 actions and the regulation of its production, the main goal in prevention and treatment of thrombotic diseases is to achieve a high PGI_2 activity at sites predisposed either to thrombosis or vascular spasm. PGI_2 has been reported to relieve ischemic pain and heal ulcers after intraarterial infusion for 3 days in patients with peripheral vascular disease.[43,44] However, the need for prolonged infusion and the hypotensive effect may present difficulties in treating patients directly with PGI_2, even if satisfactory stable analogs were developed. A more promising approach might be to use drugs that increase PGI_2 production. This approach will require a detailed understanding of the control of PGI_2 formation.

The 2 main principles operating with current drugs are: (1) that inhibition of TxA_2 production could divert endoperoxides to the synthesis of PGI_2, and (2) that inhibition of lipoxygenase activity could prevent formation of a substance capable of inhibiting PGI_2 production.

Thromboxane synthetase inhibitors are being studied because they have the advantage over cyclooxygenase inhibitors of allowing endoperoxides to accumulate and of increasing PGI_2 production. A difficulty arises because at higher doses, these drugs can inhibit cycloox

TABLE III Effect of Dazoxiben (UK-37,248) Upon 6-keto-$PGF_{1\alpha}$ Production by Bovine Aortic Endothelial Cells

	6-keto-$PGF_{1\alpha}$/10^6 cells (ng)	
Control	9.3 ± 0.2	
Dazoxiben (10^{-7} *M*)	11.2 ± 0.1	
Dazoxiben (10^{-6} *M*)	18.6 ± 0.4	p <0.001
Dazoxiben (10^{-5} *M*)	20.8 ± 0.3	p <0.001
Dazoxiben (10^{-4} *M*)	18.5 ± 0.7	p <0.001
Dazoxiben (10^{-3} *M*)	4.8 ± 0.6	

Bovine aortic endothelial cells were incubated for 1 hour and media assayed for 6-keto-$PGF_{1\alpha}$.[29]

ygenase activity. An example is illustrated in Figure 3, in which the thromboxane synthetase inhibitor dazoxiben (UK-37,248)[46,47] prevents platelet aggregation. At some concentrations of the drug, although inhibition of thromboxane synthesis is complete, platelet aggregation with arachidonic acid was unaffected, probably because of the direct aggregatory effect of the prostaglandin endoperoxide. At higher drug concentrations, arachidonate-induced aggregation was prevented, probably because endoperoxide formation was inhibited. Thus, a certain dose range existed over which thromboxane synthesis inhibition was achieved, but above that, cyclooxygenase was inhibited. The very narrow dose range of effectiveness of aspirin is shown for comparison. In studying the effect of dazoxiben on collagen-induced platelet aggregation, the 50% inhibition (IC_{50}) for the drug was 5×10^{-6} *M*,[47] similar to that for inhibition of TxB_2 production (Fig. 3).

Furthermore, in studies with cultured bovine aortic endothelial cells, the thromboxane synthesis inhibitor dazoxiben caused an increase in PGI_2 production, but high concentrations (10^{-3} *M*) reduced PGI_2 production (Table III). Such data might indicate that endoperoxide in endothelial cells can be diverted from synthesis of TxA_2 to PGI_2. Indeed, there is evidence for production of TxA_2 in cultured calf aortic endothelial cells[48] and from our own observations (Nolan RD and Martin TJ, unpublished data) with bovine aortic endothelial cells. If TxA_2 synthesis inhibition is to be applied optimally, the properties of the drugs must be examined relative to their selectivity as thromboxane synthesis inhibitors and the practical ease with which cyclooxygenase inhibition can be avoided. This will probably be achieved and part of a pharmacologic approach to the prevention of vascular occlusion will be thromboxane synthesis inhibition.

Lipoxygenase inhibition applies different principles in aiming at increased PGI_2 production. There is increasing evidence that products of the lipoxygenase pathway can inhibit PGI_2 production,[22,42,42] and it is logical to seek lipoxygenase inhibitors for the specific purpose of increasing PGI_2 formation. Again, the problem of cyclooxygenase inhibition arises, and it may be very difficult to find a lipoxygenase inhibitor that is not also a cyclooxygenase inhibitor. Nafazatrom (Bay g 6575) is an effective inhibitor of lipoxygenase. It has no direct effects on platelets, but has been shown to elevate the PGI_2 production of diabetic blood vessel in vitro.[49] Determining whether this will be of therapeutic benefit requires careful evaluation, but the observation raises interesting questions regarding the mechanisms of decreased PGI_2 production in diabetes.

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Prostacyclin Produced by the Pericardium and Its Influence on Coronary Vascular Tone

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To determine the influence of pericardial fluid prostacyclin on coronary blood flow, the latter was measured in the circumflex artery of anesthetized dogs. Intraaortic infusions of angiotensin II (25 ng·kg^{-1}·min^{-1}) reduced blood flow and released prostacyclin into pericardial fluid. Epicardial and pericardial superfusion with indomethacin (1 μg/ml) abolished prostacyclin release and significantly increased the coronary vasoconstrictor effect of angiotensin II; this treatment did not appear to affect vascular synthesis of prostacyclin. Pericardial prostacyclin may modulate the coronary vasoconstrictor effect of angiotensin, but its general role as a regulator of coronary vascular resistance is probably limited. A more important effect of pericardial prostacyclin may be exerted on the large coronary vessels in the epicardial surface. Release of prostacyclin into pericardial fluid represents a potential mechanism for opposing coronary vasospasm, especially if platelet activation is found to be a contributory factor in vasotonic angina pectoris.

Although it has long been known that the heart can produce prostanoids,[1,2] until recently the coronary vasculature was considered the only important local site of prostanoid biosynthesis.[3] However, some recent evidence has revealed the production of PGE_2 and $PGF_{2\alpha}$ by isolated cardiac myocytes, whereas PGE_2, $PGF_{2\alpha}$ and prostacyclin (PGI_2) may be produced by cardiac mesenchymal cells.[4,5] The role of cardiac prostanoids in function of the normal and ischemic heart has not been clearly resolved despite intensive investigation.[1,2]

In 1979, Herman et al[6] found that the pericardium and other serous membranes that are lined with mesothelium spontaneously generate a prostacyclin-like substance in vitro. They reported that mesothelial cells are derived from the same stem cells (the mesenchyme) as vascular endothelial cells, an important source of prostacyclin in the blood vessel wall.[7] We became interested in this potential source of prostacyclin because Dusting et al[8] had shown that topical application of prostacyclin to the left ventricular epicardium increases coronary blood flow. Moreover, prostacyclin and PGE_2 applied epicardially in low doses, potentiate a nociceptive pressor chemoreflex elicited from the epicardium in anesthetized dogs.[9,10] In this report, we review the evidence that the parietal pericardium and epicardial surface (containing visceral pericardium) are major producers of prostacyclin in vivo, and that the output of prostacyclin into pericardial fluid is increased by increasing cardiac work load.[11] We further show that pericardial production of prostacyclin is sufficient to influence coronary blood flow under some circumstances, but its most important effect may be to oppose vasoconstrictor influences on the large coronary vessels in the epicardial surface, because these vessels are normally in contact with pericardial fluid.

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Methods

Incubation of pericardium and heart slices: Samples of bovine pericardium were obtained immediately after slaughter, transported to the laboratory in cold Krebs' solution, and processed within 2 hours. Dog and rat pericardial samples were treated similarly after killing the animals. Pieces of parietal pericardium from dog, ox and rat were incubated in Krebs' solution at 22°C for 60 minutes in the presence of arachidonic acid (10 μg/ml). Dog and ox pericardium were also incubated without arachidonic acid.

Slices (0.5 to 1.0 mm) of dog hearts were prepared using a Stadie-Riggs microtome. The slices were preincubated for 60 minutes at 22°C in Krebs' solution before experimental incubations were begun. Slices of epicardium (which included

visceral pericardium), myocardium and endocardium and pieces of parietal pericardium were incubated in Krebs' solution at 22° for 60 minutes in the presence of arachidonic acid (1 μg/ml). Zero time incubation samples were taken immediately after addition of tissue.

Anesthetized dog experiments: Mongrel dogs and greyhounds (10 to 35 kg) were anesthetized with thiopental (25 to 30 mg/kg, intravenously) followed by alpha-chloralose (80 to 100 mg/kg, intravenously) as required. Dogs were artificially ventilated with air that contained additional oxygen to maintain arterial blood pH and gases in the following ranges: pH 7.25 to 7.36, oxygen partial pressure 150 to 225 mm Hg, carbon dioxide partial pressure 25 to 37 mm Hg. Arterial pressure was measured from a catheter in a femoral artery and heart rate was determined by the pulse interval using a cardiotachometer coupler. The chest was opened in the fifth intercostal space and the pericardium was opened into a cradle, with care taken to minimize leakage of blood into the pericardial sac. Drugs were infused into a femoral vein and into the epicardial irrigating fluid (see below). Coronary blood flow was measured in the circumflex branch of the left coronary artery of greyhounds using a Statham electromagnetic flow probe (2.0 to 2.5 mm) and flowmeter (SP 2202). A catheter, introduced for infusions of drugs into the coronary circulation, was passed retrogradely down the right carotid artery so that its tip lay in the aortic root. All recordings were made on a Grass model 7 polygraph.

Epicardial irrigation: In most dogs, the left ventricular epicardium was irrigated in situ at 3 ml/min with warmed (37°C) oxygenated Krebs' solution as described previously.[11] The fluid was continuously withdrawn from the pericardial cradle beneath the heart and passed over bioassay tissues.[11] Alternatively, samples of this fluid were taken for analysis into tubes that contained indomethacin (10 μg/ml), kept at room temperature for 60 minutes, and then stored frozen until extraction.

Measurement of arachidonic acid metabolites: Irrigation fluid from the dog hearts and the media from the incubations of dog, ox and rat pericardium were acidified to pH 3.5 with 1 *M* formic acid and extracted with 3 volumes of ethyl acetate. The organic layer was evaporated under nitrogen at 30°C and resuspended in column solvent for high-pressure liquid chromatography as described previously.[12] Fractions of 2 ml were collected, lyophilized and assayed by radioimmunoassay for 6-oxo-$PGF_{1\alpha}$, thromboxane B_2 (TxB_2), $PGF_{2\alpha}$ and PGE_2. Recoveries of added [^{3}H] 6-oxo-$PGF_{1\alpha}$, [^{3}H] TxB_2, [^{3}H] $PGF_{2\alpha}$ and [^{3}H] PGE_2 were monitored and data were corrected for the average loss. Recoveries were 57 ± 2, 72 ± 7, 60 ± 6 and 53 ± 2% (mean ± standard error of the mean [SEM], n = 5) for 6-oxo-$PGF_{1\alpha}$, TxB_2, $PGF_{2\alpha}$ and PGE_2, respectively. In no case did the acidification and extraction procedure generate radioactivity with chromatographic behavior other than that of the authentic prostanoid.

The 6-oxo-$PGF_{1\alpha}$ and PGE_2 levels in the medium from incubation of slices of canine heart were determined by direct radioimmunoassay of the medium without separation by high-pressure liquid chromatography.

Radioimmunoassay: Fractions corresponding to the elution volumes of each of the 4 tritiated prostanoid markers were resuspended in Tris-gelatin buffer (15 m*M* Tris-hydrochloride, 140 m*M* sodium chloride, gelatin 500 mg/liter, pH 7.4) and analyzed by radioimmunoassay as described previously.[12] Samples analyzed by direct radioimmunoassay were assayed in Krebs' solution with a standard curve diluted in Krebs solution. Sensitivities and cross-reactivities of the assays have been reported in detail.[12]

Materials: Prostaglandins and their metabolites were gifts from Dr. J. E. Pike of the Upjohn Co. Arachidonic acid (Sigma grade 1) was stored in n-hexane (10 mg/ml) under nitrogen at −20°C. Immediately before use the solvent was evaporated under nitrogen and the arachidonic acid dissolved in 0.1 *M*

TABLE I Metabolites of Arachidonic Acid Produced by Dog, Ox and Rat Pericardium In Vitro

Species	Treatment	Metabolites (ng/100 mg of Tissue) 6-oxo-$PGF_{1\alpha}$	TxB_2	$PGF_{2\alpha}$	PGE_2
Dog	Basal AA	10.6	1.3	0.8	0.2
		112.3	7.2	15.8	58.6
Ox	Basal AA	0.8	<0.1	*	0.4
		25.0	2.1	*	23.8
Rat	AA	5.8	<0.1	*	0.3

* Assay not done.

Pieces of dog pericardium (500 mg in 12 ml), ox pericardium (330 mg in 2 ml) and rat pericardium (20 mg in 1 ml) were incubated at 22°C in Krebs' solution for 60 minutes. Amounts of arachidonic acid metabolites in the Krebs' solution were determined by radioimmunoassay after separation by high-pressure liquid chromatography.

AA = arachidonic acid (10 μg/ml); PG = prostaglandin; TxB_2 = thromboxane B_2.

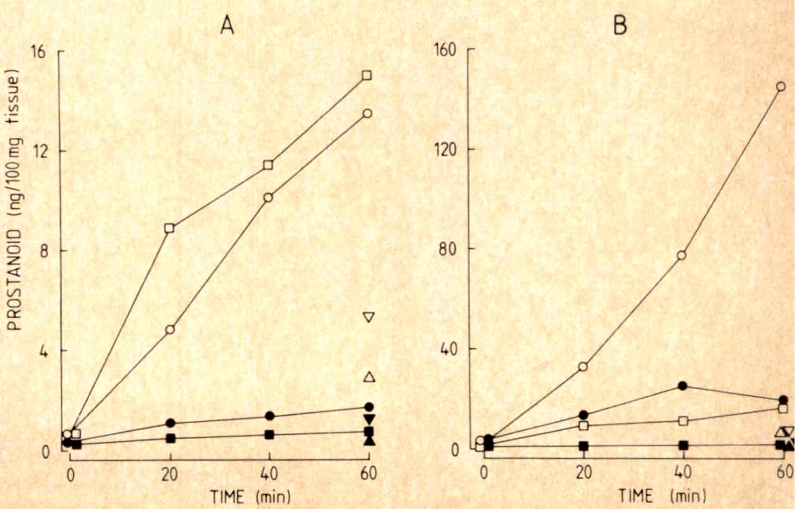

FIGURE 1. The 6-oxo-prostaglandin $F_{1\alpha}$ (**open symbols**) and prostaglandin E_2 (**closed symbols**) produced by the parietal pericardium (**circles**), epicardium (**squares**), myocardium (**triangles**) and endocardium (**inverted triangles**) of dog heart. Pieces of parietal pericardium and slices (0.5 to 1.0 mm, approximately 100 mg) of each layer of the heart were incubated at 22°C for 60 minutes in Krebs' solution. **A,** Incubation in Krebs' solution alone. **B,** Incubation in Krebs' solution containing arachidonic acid (1 μg/ml). The sensitivities of the radioimmunoassays were 1.0 and 10 pg/mg tissue for 6-oxo-$PGF_{1\alpha}$ and prostaglandin E_2, respectively.

sodium carbonate, making the sodium salt. Indomethacin (Sigma) was dissolved in 1 *M* Tris buffer (pH 8.4). Isoproterenol (Isuprel,® Winthrop) and angiotensin II (Hypertensin,® Ciba) were diluted in 0.9% (weight/volume) sodium chloride immediately before use.

Antibodies used were diluted rabbit antiserum directed against PGE_2, $PGF_{2\alpha}$ and 6-oxo-$PGF_{1\alpha}$.

Results

Prostacyclin produced by the pericardium and cardiac slices in vitro: Pieces of parietal pericardium from dog, ox and rat were incubated in Krebs' solution at 22°C with and without arachidonic acid (10 μg/ml), and prostanoids released into the incubation medium were measured by radioimmunoassay after extraction and chromatography (Table I). The hydration product of prostacyclin 6-oxo-$PGF_{1\alpha}$, was the major product detected in all species, although large amounts of PGE_2 were also produced in the presence of arachidonic acid.

The rate of prostacyclin production by the pericardium of the dog was compared with that of cardiac slices by direct radioimmunoassay of 6-oxo-$PGF_{1\alpha}$ released into the incubation medium. Pieces of parietal pericardium and slices of epicardium, myocardium and endocardium were incubated with or without added arachidonic acid (1 μg/ml) (Fig. 1). The parietal pericardium and epicardium were the most active producers of 6-oxo-$PGF_{1\alpha}$, producing more than 12 ng/100 mg of tissue after 60 minutes of incubation. Less than 2 ng of PGE_2/100 mg of tissue were produced by all tissues during these incubations. Addition of arachidonic aci greatly increased the formation of 6-oxo-$PGF_{1\alpha}$ an PGE_2 by the pericardium, but did not appreciably alte prostanoid formation by the other tissues (Fig. 1B).

Epicardial and pericardial irrigation of the dog heart in situ: Prostacyclin production has also bee studied in vivo by irrigating the left ventricular epi cardium and pericardium of the dogs' heart in situ.[1] The fluid was continuously withdrawn from the peri cardial cradle beneath the heart and either used directl to superfuse the bioassay tissues, or taken into tube containing indomethacin (10 μg/ml) for subsequen extraction, chromatography and radioimmunoassay When the fluid superfusing the bioassay tissues wa changed from fresh Krebs' solution to one that had firs irrigated the epicardium and pericardium, the bioassa tissues responded in a manner consistent with th presence of prostacyclin in the superfusate, equivalen to 2 to 10 ng/ml (Fig. 2). Epicardial irrigation wit Krebs' solution did not affect arterial pressure or hear rate. After 15 to 50 minutes of continuous epicardia irrigation, the tone of the bioassay tissues superfuse with this solution had returned to or near their base lines, suggesting that the release of the prostacyclin-lik substance from the epicardial surface had diminished Handling the heart in the pericardium when the initial effects of irrigation has subsided caused a further burst of release of the prostacyclin-like substance.

After the initial effects of epicardial irrigation had subsided, arachidonic acid (3 μg/ml) was added to the

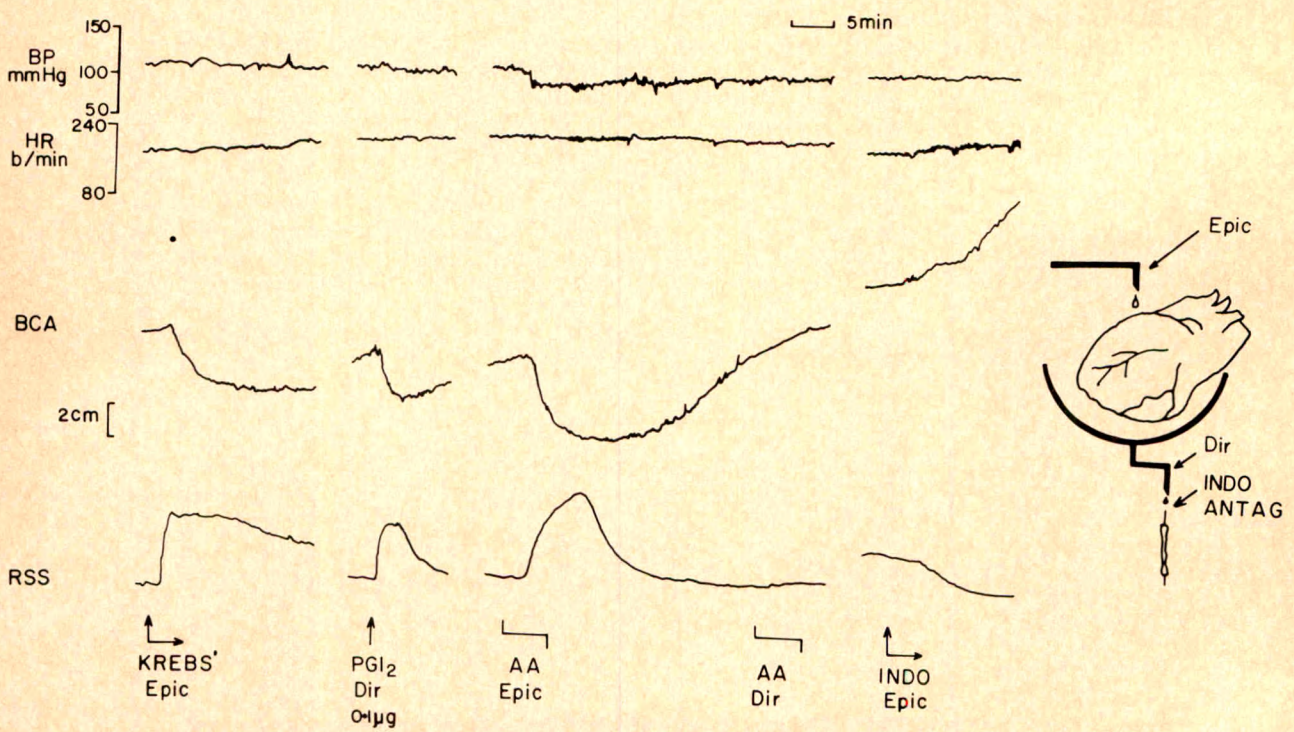

FIGURE 2. Epicardial and pericardial irrigation of a dog's heart with Krebs' solution. The records of a typical experiment are arterial blood pressure (BP), heart rate (HR) and tone of strips of bovine coronary artery (BCA) and rat stomach superfused with the irrigation fluid (RSS; see text). **Left,** the reactions of the bioassay tissues when they were superfused with Krebs' solution that had first irrigated the heart; superfusion was maintained for the rest of the experiment. The record shows the effects of addition of arachidonic acid (AA) (3 μg/ml) and indomethacin (INDO) (1 μg/ml) for the periods indicated beneath the records. Substances are added to the epicardial fluid as indicated by the diagram on the **right.** Dir = direct; Epic = epicardial; PGI_2 = prostacyclin. Reproduced from Dusting and Nolan[11] with permission of the publisher.

TABLE II Metabolites of Arachidonic Acid in the Epicardial Irrigation Fluid From Dog Heart

Sample	Arachidonic Acid Metabolites (ng/ml)			
	6-oxo-$PGF_{1\alpha}$	TxB_2	$PGF_{2\alpha}$	PGE_2
Initial sample (a)	5.6	1.6	0.5	0.5
Control isoproterenol (b)	2.8	0.7	0.1	0.8
	7.3	<0.2	0.5	0.2
Control arachidonic acid (b)	0.3	<0.2	0.1	0.2
	3.5	1.0	0.6	1.4

Samples of epicardial irrigation fluid (15 ml) were collected (a) during the first 5 minutes of irrigation (initial sample); (b) before and during intravenous infusion of isoproterenol (0.1 μg/kg/min) for 5 minutes; and (c) before and during addition of arachidonic acid (3 μg/ml) for 5 minutes to the irrigating fluid. Test samples were collected over 5 minutes, commencing 1 minute after the start of each treatment. Sixty minutes elapsed between experimental periods a, b and c. Concentrations of metabolites were determined by radioimmunoassay after separation by high-pressure liquid chromatography.
PG = prostaglandin; TxB_2 = thromboxane B_2.

irrigation fluid for 5 minutes. This reduced arterial pressure by 5 to 18 mm Hg and increased heart rate by 14 to 18 beats/min; the bioassay tissues indicated, within 1 to 3 minutes, the output of a prostacyclin-like substance[11] equivalent to >100 ng of standard prostacyclin (Fig. 2). The same concentration of arachidonic acid had no effect on the bioassay tissues when infused directly over them (Fig. 2). When arachidonic acid was added to the epicardial irrigating fluid in 2 dogs previously treated with indomethacin (10 mg/kg, intravenously), there were no effects on blood pressure, heart rate or the bioassay tissues.

After 2 to 4 hours of epicardial irrigation, indomethacin (1 μg/ml) was added to the irrigation fluid. In all experiments, this induced within 5 to 10 minutes an increase in tone of the bovine coronary artery and relaxation of the rat stomach strip (Fig. 2), but had little effect on the rat colon. Relaxation of the bovine artery induced by standard bolus doses of prostacyclin (25 to 100 ng) increased after treating the heart with indomethacin. These observations suggested that epicardial treatment with this cyclooxygenase inhibitor had prevented the release of prostacyclin into the irrigation fluid.[11]

Stimuli that increase prostacyclin release into pericardial fluid: Some maneuvers that alter systemic blood pressure or heart rate in the dog also increase release of the prostacyclin-like substance in vivo.[11] For example, intravenous infusions of isoproterenol (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 minutes), which increased heart rate by 33 ± 5 beats/min and reduced mean arterial pressure by 18 ± 2 mm Hg (mean ± SEM, n = 8), increased release of the prostacyclin-like substance into the epicardial irrigating fluid, equivalent to 50 to 100 ng of prostacyclin (Fig. 3). Addition of indomethacin (1 μg/ml) to the irrigating fluid abolished release of the substance (Fig. 3), as did intravenous propranolol (0.5 mg/kg). Radioimmunoassay confirmed that prostacy-

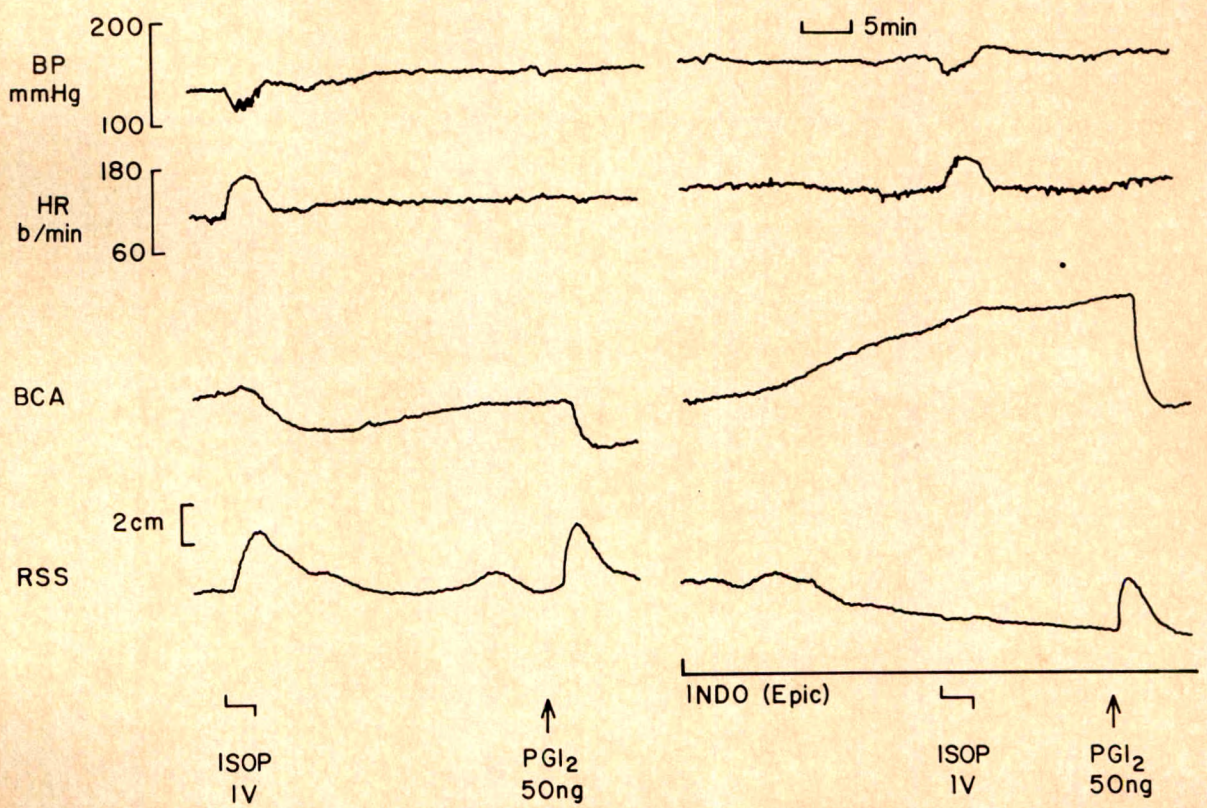

FIGURE 3. Effect of intravenous infusions of isoprenaline (ISOP) (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on output of the prostacyclin (PGI_2)-like substance into the epicardial irrigation fluid. Records are as in Figure 2. In the **second panel,** epicardial indomethacin (INDO Epic) (1 μg/ml) is superfused over the heart instead of directly over the bioassay tissues. BCA = bovine coronary artery; BP = blood pressure; Dir = direct; Epic = epicardial; HR = heart rate; INDO = indomethacin; RSS = rat stomach strip. Reproduced from Dusting and Nolan[11] with permission of the publisher.

TABLE III Effects of Angiotensin Infusions on Coronary Blood Flow After Indomethacin

	Control		Epicardial Indomethacin		Intravenous Indomethacin	
	Resting	AII Response* (%)	Resting	AII Response* (%)	Resting	AII Response* (%)
mBP (mm Hg)	132 ± 6	23 ± 6	135 ± 7	21 ± 5	149 ± 14†	16 ± 9
mCBF (ml/min)	89 ± 17	−3 ± 5	87 ± 15	−12 ± 4†	69 ± 7	−19 ± 7†

* Responses measured as percentage of resting blood pressure and coronary blood flow in each case.
† Significantly different from control values ($p < 0.05$ paired Student t test).
Angiotensin II was infused in 5 dogs intraarterially at 25 $ng \cdot kg^{-1} \cdot min^{-1}$ during a control period, during epicardial superfusion with indomethaci (1 $\mu g/ml$) and in 3 of these dogs after intravenous indomethacin (5 mg/kg). Values are mean ± standard error of the mean.
AII = angiotensin II; mBP = mean arterial blood pressure; mCBF = mean coronary blood flow.

clin, measured as 6-oxo-$PGF_{1\alpha}$, was the major, if not the only, prostanoid released into the epicardial fluid by stimulation with isoproterenol (Table II).

The effects of isoproterenol may have been a result of its action on heart rate, because in 5 dogs whose heart rates were controlled by right atrial pacing, increasing the rate abruptly by 60 to 90 beats/min also released the prostacyclin-like substance, equivalent to 50 to 100 ng of prostacyclin. However, stimuli that increase afterload have also been found to release this substance, including aortic constriction, angiotensin infusions (0.02 to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenously), and bilateral carotid occlusion.[11] All of these stimuli increase cardiac work (calculated as mean arterial pressure/heart rate product) and cause increased stretching of the pericardium and epicardium. Intravenous indomethacin (5 to 10 mg/kg) and aspirin (50 mg/kg) also abolished release o the prostacyclin-like substance.[11]

Chromatography and radioimmunoassay of un diluted pericardial fluid and epicardial irrigatio fluid: Approximately 2 ml of pericardial fluid could b withdrawn from dogs immediately after opening th pericardial sac. The concentrations of all prostanoid in pericardial fluid showed wide variation between in dividual dogs, but 6-oxo-$PGF_{1\alpha}$ was always the pre dominant prostanoid detected. The concentrations o this prostanoid ranged from 1 to >30 ng/ml, as deter mined by radioimmunoassay after extraction anc chromatography. The mean concentrations of 6-oxo $PGF_{1\alpha}$, PGE_2, $PGF_{2\alpha}$ and TxB_2 in pericardial fluid o 8 dogs were 5.9 ± 2.8, 0.18 ± 0.14, 0.18 ± 0.11 and 0.2 ± 0.22 ng/ml (± SEM), respectively.

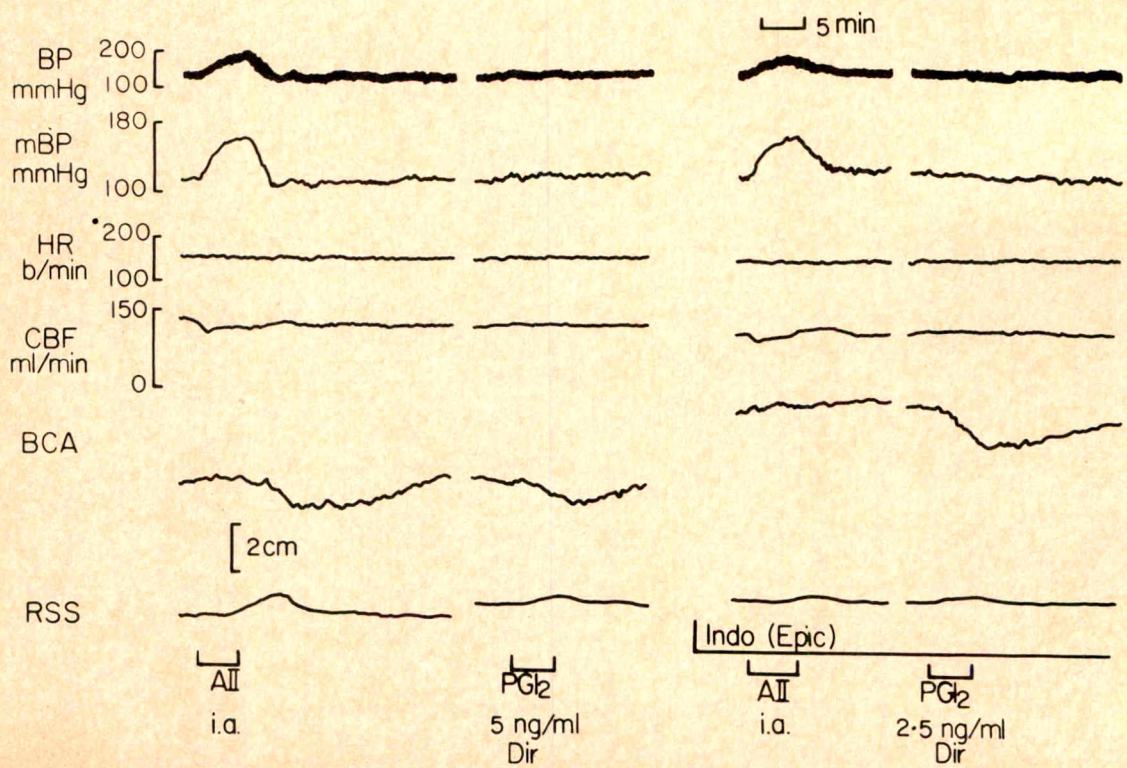

FIGURE 4. Effect of epicardial indomethacin (Indo Epic) (1 $\mu g/ml$) on the coronary blood flow (CBF) and release of the prostacyclin (PGI_2)-like substance induced by intraaortic angiotensin II (AII) (25 $ng \cdot kg^{-1} \cdot min^{-1}$) in an anesthetized dog. Records are as in Figure 2 with the addition of phasic blood pressure (BP) and blood flow in the circumflex artery, measured with a 2.0-mm electromagnetic probe. BCA = bovine coronary artery; Dir = direct; HR = heart rate; i.a. = intraaortic; mBP = mean BP; RSS = rat stomach strip.

Samples of epicardial irrigation fluid collected during the first 5 minutes of irrigation contained more 6-oxo-$PGF_{1\alpha}$ than the total amount of PGE_2, $PGF_{2\alpha}$ and TxB_2, as measured by radioimmunoassay (Table II). After 120 minutes of epicardial and pericardial irrigation, addition of arachidonic acid to the irrigating fluid increased the release of all prostanoids, although 6-oxo-$PGF_{1\alpha}$ remained predominant (Table II).

Pericardial prostacyclin and coronary blood flow: Infusions of angiotensin II (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 minutes) into the aortic root increased arterial pressure, reduced heart rate, and released a prostacyclin-like substance into epicardial irrigation fluid. Coronary blood flow, measured in the circumflex artery, was reduced slightly in most dogs (Fig. 4). The mean increases in arterial pressure and changes in mean blood flow at the end of the infusion periods are shown in Table III. Epicardial and pericardial superfusion with indomethacin (1 μg/ml) did not change resting arterial pressure or blood flow, but abolished angiotensin-induced release of prostacyclin (Fig. 4) and significantly increased ($p < 0.05$, paired Student t test) the coronary vasoconstrictor response (Table III). After intravenous infusion of indomethacin (5 mg/kg), the decrease in coronary blood flow induced by angiotensin was also greater than that in the control period, but the pressor response was not changed (Table III).

The effect of indomethacin on coronary blood flow responses to arachidonic acid was also studied. Intraaortic injections of arachidonic acid (100 μg/kg) caused rapid, transient increases of blood flow followed by hypotension and tachycardia (Fig. 5). In only 3 of 10 dogs was there any indication of prostanoid release into the pericardial irrigation fluid; this amounted to <50 ng of standard prostacyclin. Epicardial superfusion with indomethacin (1 μg/ml) did not significantly alter the coronary vasodilator or hypotensive effect of arachidonic acid, but intravenous indomethacin (5 mg/kg) greatly reduced the flow response and abolished the hypotension (Fig. 5).

Discussion

Source of prostacyclin in pericardial fluid: Microsomes of myocardium are much weaker producers of prostaglandins[13–15] than those of blood vessels.[16] Moreover, prostacyclin is the major metabolite of arachidonic acid released both from isolated coronary arteries and from Langendorff-perfused hearts.[17–20] Thus, Sivakoff et al[3] concluded that the coronary vasculature, rather than myocytes, was the primary site of cardiac prostaglandin synthesis. We have clearly shown that high concentrations of a prostacyclin-like substance and 6-oxo-$PGF_{1\alpha}$ (the degradation product of prostacyclin) are released into pericardial fluid in vivo, and only much smaller amounts of other prostanoids can be detected. However, several pieces of evidence suggest that the coronary vasculature is not a major source of pericardial fluid prostacyclin. First, epicardial and pericardial superfusion with indomethacin abolished the release of prostacyclin into the irrigation fluid. However, this treatment did not alter the coronary vasodilator effects of arachidonic acid administered into the vascular compartment, suggesting that the inhibitor did not penetrate to the cyclooxygenase in the coronary vasculature. Second, intravenous infusions of prostacyclin at rates achieving supraphysiologic concentrations in the bloodstream were not accompanied by detectable increases of prostacyclin in the irrigation fluid.[11] Third, we have confirmed that myocardium is a relatively poor producer of prostanoids in general and prostacyclin in particular, whereas the parietal pericardium and the epicardial surface are very active producers of prostacyclin in vitro. Furthermore, Ahumada et al[5] found that a pure cell line of rat myocytes grown in culture can produce only PGE_2 and $PGF_{2\alpha}$, whereas undifferentiated cardiac mesenchymal cells may produce, in addition, small amounts of 6-oxo-$PGF_{1\alpha}$. Therefore, it appears that prostacyclin in pericardial fluid is most likely derived from the serous membranes of the parietal pericardium and the epicardial surface. Mesothelial cells may be the primary cell source of this substance.[6]

Prostacyclin and regulation of coronary blood flow: In anesthetized dogs, prostacyclin is a potent coronary vasodilator when it is given intravascularly, and even when it is applied topically onto the epicardial surface.[8] The role of prostaglandins in regulation of coronary blood flow has been the subject of many investigations; the general conclusion has been that although prostaglandins are released into coronary venous blood during hypoxia and ischemia, they are neither essential nor contributory to the resulting increased blood flow.[1,2,21] One possible exception is the reactive hyperemia after prolonged periods (≥10 minutes) of coronary artery occlusion,[1,2] for this response is associated with release of PGE_2 and $PGF_{2\alpha}$ from the ischemic zone,[22] and both prostaglandin release and hyperemia are attenuated by pretreatment with indomethacin.[23,24]

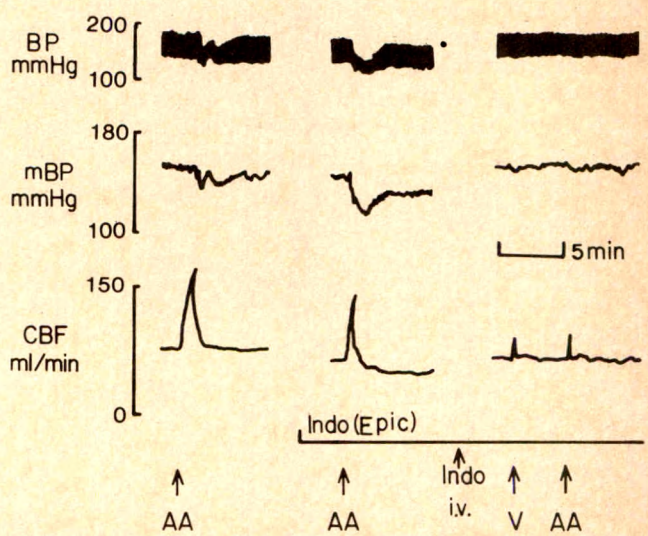

FIGURE 5. Effects of epicardial indomethacin (Indo) on a typical coronary blood flow (CBF) response to intraaortic injection of arachidonic acid (AA) (100 μg/kg). Indomethacin is given epicardially (Epic) (1 μg/ml) and intravenously (5 mg/kg) at the points indicated beneath the records. BP = blood pressure; mBP = mean BP; v = vehicle used for arachidonic acid.

Another role for cardiac prostanoids may be modulation of the coronary vasoconstrictor influence of activation of the renin-angiotensin system. Angiotensin II is known to stimulate prostacyclin release in most vascular beds,[20,25,26] including the lungs[27,28] and coronary circulation.[20] Furthermore, since angiotensin is a weak constrictor of the coronary circulation, it has been suggested that vascular prostacyclin attenuates the effects of the peptide.[20,25–29] Hintze and Kaley,[30] however, did not observe potentiation by indomethacin of the vasoconstrictor effect of angiotensin injected locally into the coronary artery of dogs. In contrast, Gunther and Cannon[31] reported marked enhancement by indomethacin of the coronary vasoconstrictor effect in the left ventricular wall, suggesting that systemic actions of the peptide were involved in stimulating release of a prostanoid modulator. We have shown that topical application of indomethacin onto the epicardial surface also increases the vasoconstrictor effect of angiotensin on coronary resistance vessels. We therefore suggest that prostacyclin of epicardial or pericardial origin modulates coronary vascular tone under these conditions.

Prostacyclin release into pericardial fluid was also stimulated by factors that increased afterload or heart rate. Increases of afterload that result in increased end-diastolic volume cause increased stretching of the epicardium and pericardium, and thereby increase friction between the pericardial surfaces. Such mechanical events may be the final common mechanism for increasing prostacyclin release, for manipulation of the heart in the pericardial sac also increased the release of prostacyclin.[11] Certainly, stretching of isolated blood vessels and cutting vessel rings increases the output of prostacyclin from these tissues.[32,33] Therefore, pericardial prostacyclin might also contribute to coronary vasodilation under other circumstances when afterload or heart rate is increased.

Pericardial prostacyclin does not, however, influence the coronary vascular response to all stimuli that increase its release. Experiments in isolated rabbit hearts indicate that prostanoids mediate the coronary vasodilator effects of bradykinin.[3,29] Intraaortic infusion of bradykinin also releases prostacyclin into the epicardial irrigation fluid, an effect partly related to the reflex tachycardia and partly to direct activation of phospholipase (Woodman DL, Dusting GJ, and Nolan RD, unpublished observations). Coronary vascular resistance was reduced by bradykinin, but this effect of the peptide was not sustained. Furthermore, although topical indomethacin (1 μg/ml) abolished bradykinin-induced release of prostacyclin, the coronary vascular response to bradykinin was not altered (Woodman et al, unpublished observations). Therefore, pericardial release of prostacyclin does not contribute to the coronary vasodilator action of bradykinin.

Possible roles of pericardial prostacyclin in myocardial ischemia: That bradykinin releases prostacyclin from the epicardial surface might have other consequences for myocardial ischemia. Bradykinin is generated in the ischemic myocardium and can be found in coronary sinus blood samples after coronary artery occlusion.[34] This peptide may have a local role in redistribution of coronary blood flow after infar tion,[29] but in addition, it stimulates sensory nerv endings in the ventricular wall.[35,36] Since bradykinin a potent pain-producing (algesic) substance, and i epicardial application also elicits sympathetic press reflexes accompanied by tachycardia, it has been su gested that bradykinin causes the pain and reflex even that accompany attacks of angina pectoris.[37] Furthe more, prostacyclin and PGE_2 are hyperalgesic,[38] an epicardial application of these prostanoids sensitize chemosensitive nerve endings and potentiates the refle increases in arterial pressure and heart rate induced b bradykinin.[9,10,37] Indomethacin has the opposite actio reducing pain and bradykinin-induced pressor reflex es.[37] Staszewska-Barczak and colleagues[9,10] propose that endogenous prostacyclin, released in the ischemi left ventricular epicardium after bradykinin generatio may act in concert with the peptide to signal angina Prostacyclin of pericardial origin may also sensitiz afferent nerves to the pain-producing effect of brady kinin in pericardial inflammation. The increased releas of prostacyclin into pericardial fluid may thus be factor in initiating the nociceptive response, as warning that an inappropriate stimulus to the hear should be withdrawn.

Others have suggested that prostacyclin may also b released from the ischemic myocardium itself and tha it may protect against early postinfarction arrhyth mias,[39,40] limit ischemic damage[41] and reduce infarc size.[42] Whether prostacyclin released into the pericar dial fluid may confer similar protective effects on th heart is not known. A mechanism that might contribut to protection of the ischemic myocardium involves fa cilitation of depressor chemoreflexes of vagal origin, a action which prostacyclin has been found to exert whe infused into the circulation.[9] Predominance of vaga reflexes reduces sympathetically mediated pressor re flexes and sympathetic drive to the heart, thereby re ducing the cardiac work load and oxygen demand. Pericardial prostacyclin, however, is unlikely to exer this type of action, because it does not influence vaga reflexes when applied epicardially. The functions o endogenous prostacyclin in the ischemic heart clearly require further study.

Pericardial prostacyclin and large coronary vessel tone: The suggestion that thromboxane A (TxA_2) may evoke coronary artery spasm in humans has attracted great interest. Platelet activation apparently occurs during vasotonic angina,[43] and elevated levels o TxB_2 (the hydration product of TxA_2) have been found in peripheral blood[44] and coronary sinus blood from patients with variant angina.[45] Prostacyclin is an endogenous physiologic antagonist of TxA_2, and coronary vasoconstriction might equally result from a deficiency of prostacyclin formation. The coronary vascular site of prostacyclin biosynthesis is obviously of considerable importance in this regard. However, the large coronary vessels in which vasospasm occurs are located in the epicardial surface, with only a serous membrane and adventitia separating the vascular smooth muscle from the pericardial space. The tone of these vessels may well be influenced by the very high concentrations of prostacyclin found in pericardial fluid. Aiken et al[46] showed

that topical application of prostacyclin over partially obstructed coronary vessels in dogs prevented platelet thrombi forming in these vessels at the sites of obstruction. Furthermore, it has recently been reported that indomethacin reduces coronary blood flow in patients with obstructions of the left coronary artery.[47]

Thus, pericardial fluid prostacyclin might represent an important mechanism for preventing constriction of the large coronary vessels, especially if platelet activation is a contributory factor to vasospasm. Moreover, if the coronary vessels are atheromatous, the capacity to stimulate pharmacologically the vascular synthesis of prostacyclin may be very much reduced,[13,48] whereas the pericardial site of synthesis is less likely to be impaired. Our studies indicate that therapeutic interventions might usefully take account of endogenous prostacyclin produced by the pericardium.

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Prostanoids and Cardiac Reflexes of Sympathetic and Vagal Origin

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Prostaglandins in concentrations too low to stimulate afferent nerve endings in the heart may sensitize them to chemical or mechanical stimuli that activate cardiac reflexes during myocardial ischemia. Bradykinin, which is released from the heart during ischemia, elicits sympathetically mediated reflex pressor effects and tachycardia when applied in low doses (0.1 to 1 μg) to the epicardium of the left ventricle in open-chest, anesthetized dogs. The reflex pressor effects evoked by bradykinin are reduced after inhibition of prostaglandins biosynthesis with indomethacin and potentiated by concomitant topical application of low doses (0.1 to 0.3 μg/min) of PGE_1 or PGE_2 and prostacyclin (PGI_2). The pressor and tachycardic responses to bradykinin are also enhanced after temporary (10-minute) coronary occlusion; this potentiation is abolished by indomethacin treatment and can be restored by superfusing the ventricle with prostaglandins. Nicotine is known to excite mechanosensitive vagal receptors with afferent C fibers, which supply the left ventricle, and to elicit reflex hypotension and bradycardia. This depressor vagal reflex evoked by epicardial or intracoronary administration of nicotine (10 to 50 μg) was not affected by either indomethacin or by topical application of PGE_1, PGE_2, or PGI_2. Also, intracoronary infusion of PGE_2 (0.1 to 0.3 μg/min), which enhanced the pressor reflex effects of bradykinin, was without effect on nicotine-induced depressor reflex. However, intracoronary infusion of PGI_2 (0.1 to 0.3 μg/min) significantly enhanced the hypotensive and bradycardic responses to nicotine and, at the same time, reduced sympathetically mediated reflex effects of bradykinin. The hypotensive effects induced by epicardial or intracoronary administration of nicotine were also significantly enhanced during intravenous infusion of subdepressor doses of PGI_2 (5 to 20 ng/kg/min). Treatment with captopril, which enhances the endogenous production of prostaglandins, greatly enhanced the reflex depressor effects of nicotine; this potentiating effect of captopril was completely abolished by indomethacin treatment. An increase in the magnitude of nicotine-induced reflex depressor effects was also observed after intravenous injection (1 μg/kg) or infusion (25 to 50 ng/kg/min) of prostaglandin D_2. A working hypothesis is proposed to account for the role of prostanoids in activation of cardiac reflexes during myocardial ischemia.

Cardiac reflexes, together with reflexes arising from the respiratory system and arterial baro- and chemoreceptors, play an important role in the regulation of volume and pressure.[1] Cardiac reflexes are also considered an important factor in human pathophysiology, particularly in conditions such as coronary heart disease,[2–5] congestive heart failure[6] or hemorrhage.[7]

Cardiac reflexes originate from a variety of sensory receptors present in all 4 cardiac chambers and the coronary arteries. The receptors are connected to myelinated and unmyelinated afferent fibers that run centrally by way of 2 separate pathways, 1 with the vagus nerves to the medulla and 1 with the cardiac sympathetic nerves to the upper thoracic segments of the spinal cord.[8] There are many important differences in anatomic distribution, functional characteristics, and reflex properties of cardiac receptors associated with the 2 afferent systems innervating the heart; these were reviewed in detail by Coleridge and co-workers.[9–11] Briefly, receptors associated with afferent fibers in cardiac sympathetic nerves and cell bodies in the dorsal root ganglia provide a widespread, continuous sensory innervation of the surface of the heart that extends to the roots of the great vessels and the parietal pericardium. This widespread and diffuse distribution of the sympathetic afferent innervation contrasts with the

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more restricted distribution of the vagal afferent system, which is generally more selective.

Receptors connected to myelinated vagal afferent fibers innervate mainly the low-pressure chambers and are confined predominantly to the atriovenous junctions.[12] The ventricles receive relatively few myelinated but many unmyelinated afferent fibers from the vagus. The endings with the afferent C fibers are particularly numerous in the left ventricle and are situated in the epicardium and at all depths of the ventricular epicardium.[9,10] Nerve endings with myelinated vagal afferents are mechanoreceptors. Those located in the myocardium of both ventricles and around the left coronary artery discharge during ventricular systole and this increases with increasing ventricular pressure.[12] Ventricular endings with unmyelinated afferents, on the other hand, have a sparse and irregular discharge at normal cardiovascular pressures. Many of these endings are mechanosensitive and respond with increased firing, usually in systole, to increases in end-diastolic pressure, ventricular wall tension, and during vigorous beating produced by epinephrine.[13,14] These mechanosensitive vagal receptors with C-fiber afferents are also susceptible to chemical stimulation. They are activated by intracoronary or epicardial application of nicotine and veratroidine and elicit reflex decreases in the heart rate and arterial pressure.[15] There is another group of vagal unmyelinated afferent endings which are little sensitive to mechanical stimulation produced by changes in cardiac volume or pressure, but are excited by foreign chemicals, such as phenyl diguanide and capsaicin,[9,10] and by endogenous substances, such as bradykinin[16] and prostaglandins.[17,18] For this group of afferent receptors, the term "chemosensitive endings" has been proposed by Coleridge and Coleridge[10,11] to distinguish them from the conventional chemoreceptors, since they are not stimulated by hypoxia or cyanide.

Myelinated and unmyelinated afferent fibers traveling in the cardiac sympathetic nerves and supplying the terminals in the walls of the ventricles and the coronary arteries on the surface of the heart are often silent or have a sparse discharge, comparable to that of vagal mechanoreceptors with C-fiber afferents.[8,9,11] Many of these endings are mechanosensitive and are activated by light stroking and during increases in transmural pressure.[9,19] However, the frequency of discharge evoked by even a large increase in transmural pressure is usually low and poorly sustained[19] compared with the high frequency of discharge in vagal mechanoreceptor afferents, which is well maintained for the duration of the stimulus.[9,12] The brief and relatively modest response of sympathetic afferent endings to increases in ventricular volume or pressure is in marked contrast to the high frequency of firing, lasting for several minutes, that occurs in response to stimulation evoked by endogenous chemical substances such as lactic acid, bradykinin and potassium.[9,20–23]

Cardiac reflexes arising from stimulation of vagal and sympathetic afferent endings in the ventricle are opposite in sign. Reflexes mediated by the medullary vagal input are generally inhibitory or depressor and analodiated by afferent sympathetic fibers or by the spinal input are in contrast mainly excitatory or pressor.[8,10,24–29] How the 2 afferent cardiac systems, medullary and spinal, are connected and interact at the central level is unclear.[1,30] However, several types of interaction between the 2 systems are known to operate. Vagal afferent activity arising from the heart exerts tonic inhibition on sympathetic efferent activity, particularly to the heart and kidney; this is most apparent when tonic inhibitory influences arising from the arterial baroreceptors have been minimized.[14] Activation of various vagal afferent endings that supply the ventricles by mechanical or chemical stimulation causes reductions in the heart rate and blood pressure that result from a reflexly mediated increase in vagal efferent discharge to the heart and inhibition of sympathetic efferent activity in cardiac[31] and peripheral constrictor nerves, including those to the kidney, muscle and intestinal beds.[14] Stimulation of cardiac sympathetic afferent fibers is, on the other hand, associated with reflex inhibition of cardiac vagal efferent activity and an increase in sympathetic efferent discharge to the heart.[31] There is also evidence for the existence of a cardiocardiac vagosympathetic negative feedback mechanism activated by sympathetically mediated increases in ventricular contractility.[32,33]

It is not clear whether sympathetic afferent activity arising from the heart participates in normal cardiovascular control. Unlike vagal mechanoreceptors, the endings of both myelinated and unmyelinated sympathetic afferent fibers appear to be poorly designed to provide precise continuing information about changes in mechanical performance of the cardiac pump.[11,19] However, their high sensitivity to touch, and particularly to stimulation by endogenous chemical agents, makes them well suited to signal sudden changes in cardiac metabolism and alterations in physicochemical external environment of the heart.[9,11]

Prostanoids and Cardiac Reflexes of Sympathetic Origin

Early research on the actions of prostaglandins revealed that although high doses may cause overt pain in man[34] or a pain-like response in experimental animals,[35] a typical effect of low concentrations that occur in inflammation or other forms of tissue injury such as ischemia is induction of hyperalgesia, that is, a state in which pain can be elicited by low-intensity mechanical or chemical stimulation.[34] The hyperalgesic effect, which seems to be peculiar to prostaglandins of the E type and PGI_2,[36] is attributed to their ability to sensitize sensory nerves by triggering a metabolic process that involves activation of adenyl cyclase, elevation of adenosine 3′:5′-cyclic phosphate (cyclic AMP) and calcium concentration at the nerve terminal with a subsequent decrease in the excitation threshold.[37]

Afferent fibers in the cardiac sympathetic nerves appear to be soley responsible for signaling the pain of myocardial ischemia, because the pain of angina in man and the pain-like pseudaffective response to acute coronary occlusion in conscious dogs are relieved by

thoracic ganglia, but not by vagotomy.[38,39] Sympathetic afferent endings in the heart not only signal pain, but also initiate excitatory cardiovascular reflexes, manifested by increases in arterial pressure, heart rate, ventricular contractility and myocardial excitability.[3,25,28,29,40] Hypertension and tachycardia frequently occur at the onset of anginal attacks[2,41] and myocardial infarction,[5] and there is good evidence to suggest that these excitatory reflexes can contribute to the development of arrhythmias and may even lead to ventricular fibrillation.[42]

The precise mechanism of stimulation of the sympathetic afferent nerves by myocardial ischemia is not known. Experimental studies suggested that endings associated with myelinated afferent fibers are excited mainly mechanically, by stretching and shortening of the bulging ischemic wall, whereas endings with unmyelinated afferents are stimulated mainly by chemical agents released locally during ischemia.[25,43,44]

Chemical changes associated with ischemia include accumulation of lactic acid, release of adenosine and potassium, and enhanced formation and release of bradykinin and prostaglandins.[45–51] Many of these substances, particularly bradykinin, are potent algesic agents.[52] Bradykinin applied to the surface of the left ventricle or injected into the coronary artery stimulates afferent sympathetic terminals with both A and C fibers,[21,22] and in lightly anesthetized animals, this increase in afferent activity is often accompanied by a pseudaffective response.[21,52] In anesthetized dogs[28,29] or cats,[22,53] minute doses of bradykinin (1 ng to 1 μg) applied directly to the epicardium of the left ventricle elicit dose-dependent, sympathetically mediated increases in blood pressure and heart rate. These observations, together with those of increased output of bradykinin after coronary ligation in dogs,[48] suggest that this chemical substance may have a major role in activation of sympathetic afferent nerves during ischemia. However, Uchida and Murao[20] found that treatment with trasylol, which inhibits bradykinin formation,[54,55] resulted in only slight (up to 20%) inhibition of the ischemia-induced excitation of both A and C sympathetic afferent nerves. On the other hand, pretreatment with sodium bicarbonate, to prevent acidosis, completely suppressed excitation of the unmyelinated fibers induced by coronary occlusion. Also, aspirin treatment was found to be effective in reducing ischemia-induced excitation of afferent C fiber by as much as 72%, and that of myelinated A fibers by 38%.

In another study, Uchida and Murao[21] demonstrated that stimulation of A and C sympathetic afferent fibers evoked by epicardial application of bradykinin was also significantly reduced by aspirin; they attributed this effect to the competitive occupation of chemosensitive sites at the pain receptors, as originally suggested by Guzman et al.[52] However, the discovery that aspirin-like drugs inhibit the biosynthesis of prostaglandins,[56] together with findings that prostaglandins induce hyperalgesia by sensitizing sensory nerves to mechanical and chemical stimulation[34] led to the proposal that the analgesic activity of anti-inflammatory agents such a aspirin and indomethacin is due to the removal c prostaglandin release and, hence, their sensitizing actio on sensory nerves.[34]

In agreement with the results of the action potentia studies,[21] Staszewska-Barczak et al[28] found that refle increases in blood pressure and heart rate induced b topical application of bradykinin to the left ventricle i dogs are significantly attenuated by treatment wit indomethacin. Furthermore, it was found that treat ment of the heart surface with minute amounts of PGE or PGE_2 (10 ng/min) restored reflex pressor response to bradykinin which had been reduced by indometha cin; $PGF_{2\alpha}$, in doses up to 1 μg/min, had no effect. Wit higher doses of PGE_1 (0.1 to 1 μg/min), the pressor ef fects produced by threshold doses of bradykinin (20 t 30 ng) were nearly doubled; even the reflex pressor re sponse to a maximal dose of bradykinin (1 μg) was po tentiated by almost 50%. This potentiation was stil evident at 30, and sometimes 60 minutes after prosta glandin treatment. In some experiments, the sensitivity to bradykinin was increased so much that the refle pressor effects could be evoked by doses as low as 1 ng It is noteworthy that PGE_1 and PGE_2 in doses up to 1 μg were without pressor effects by themselves.[28] Later Baker et al[57] recorded action potentials in cardiac sympathetic afferent fibers in cats and confirmed that epicardial application of PGE_1 in doses (0.1 μg) that alone did not excite nerve endings in the ventricle potentiated the stimulating effect of bradykinin on these endings.

The release of prostaglandins from the heart in response to ischemia, hypoxia or mechanical stimulation has been observed in the isolated heart preparation[5] and in intact animals with an open[49] and closed chest.[5] Recently, cardiac prostaglandin release was also demonstrated during myocardial ischemia induced by atrial pacing in patients with coronary artery disease.[51] Acute coronary occlusion in the closed-chest dog was associated with an enhanced release of PGE_2 and $PGF_{2\alpha}$. $PGF_{2\alpha}$ was found to originate only from the ischemic zone, whereas PGE_2 was released from the ischemic as well as the nonischemic myocardium.[50] As PGE_2 and $PGF_{2\alpha}$ are synthesized mainly by the cardiac myocytes,[59] it is possible that abnormal stretching and shortening of the ischemic zone, as well as a compensatory increase in contractions of the nonischemic myocardium, were mainly responsible for stimulating an increased synthesis and release of these prostaglandins. In our experiments,[28] pronounced increases in the magnitude of reflex pressor and tachycardic responses to epicardial bradykinin were observed after temporary (10-minute) coronary occlusion. The degree of potentiation resulting from regional myocardial ischemia was comparable with that produced by application of higher doses of PGE_1 (1 μg/min). The potentiating effect of ischemia could be abolished by pretreatment with indomethacin and then restored by superfusing the ischemic area with PGE_1 or PGE_2. These results, together with observations that postocclusion augmentation of impulse activity in sympathetic

ished by aspirin,[20] clearly indicated that locally released prostaglandins were mainly responsible for ischemia-induced potentiation of the afferent nervous activity and the reflex effects of bradykinin.

PGI_2 is the product of the conversion of prostaglandin endoperoxides by a microsomal enzyme, PGI_2 synthetase, which is most highly concentrated in the vascular endothelial cells. All vascular tissues, including coronary vasculature, from all species so far tested were found to generate and release PGI_2 predominantly.[60,61] However, other tissues, such as pericardium and peritoneum, which are covered by a layer of the squamous epithelial cells (the so-called mesothelium), can also generate high amounts of PGI_2.[62] PGI_2 presumably formed by the epicardial mesothelium is also released during superfusion of the dog's heart in situ with Krebs' solution and the output of PGI_2 into the perfusate is markedly enhanced by mechanical stimulation of the surface of the heart, as well as by increases in cardiac work induced by aortic constriction, bilateral carotid occlusion, or intravenous administration of pressor doses of angiotensin.[63]

Recently, Ferreira et al[36] found that PGI_2, like PGE_2, can induce hyperalgesia. They also showed that the hyperalgesic effect of PGI_2 is quick in onset but short-lasting, whereas hyperalgesia caused by PGE_2 develops more slowly but is prolonged. Our studies[64–66] have shown that PGI_2 significantly potentiated the reflex pressor effects of bradykinin when applied in low doses (0.1 to 0.3 μg/min) directly to the surface of the left ventricle in dogs, but not when infused in equal doses into the coronary artery. In this respect, the action of PGI_2 differed from that of PGE_2, which was equally effective in enhancing the reflex effects of bradykinin, whether applied topically or infused into the coronary blood supply to the left ventricle. Also, the duration of the potentiating effect, unlike that of PGE_2, was extremely brief and disappeared as soon as application of PGI_2 was discontinued. These observations led us to propose that PGI_2 released by the epicardial or pericardial mesothelium or both may contribute to the signaling of pain and excitatory cardiovascular reflexes when kinin formation occurs during myocardial ischemia or pericardial inflammation.[66]

Prostanoids and Cardiac Reflexes of Vagal Origin

Recently, Hintze,[67] Chapple,[68] and their co-workers found that the hypotension induced by intravenous, intracoronary, or left atrial injections of high doses of PGI_2 (10 to 30 mg) in dogs is frequently accompanied by bradycardia. In contrast, the hypotension induced with equal or higher doses of PGE_2 is always closely followed by tachycardia, presumably through a baroreflex mechanism. Observations that bradycardia induced by PGI_2 was reduced or abolished by atropine suggested that a reflexly mediated increase in vagal efferent discharge to the heart, rather than a direct effect of PGI_2 on cardiac pacemaker cells, was responsible for the bradycardic effect. Because bilateral vagotomy not only reversed the bradycardia, but also reduced the hypotensive response, these investigators[67,68] proposed that the afferent pathway of the reflex was also in the vagus and that at least part of the hypotensive actio of PGI_2 is also reflexly mediated.

Subsequent action potential studies showed that hig doses of PGI_2 (1 to 20 μg) injected into the left atriu in dogs stimulated vagal afferent C fibers with chemo sensitive endings in the ventricle.[18] High doses of PGE (1 to 5 μg/kg) and bradykinin (0.3 to 1 μg/kg) injecte into the left atrium also stimulated chemosensitiv vagal afferent endings in the atriums, ventricles an adjacent great veins and arteries.[16,17] The stimulator effect appeared to be specific for chemosensitive vaga endings, since neither afferent C fibers of mechano sensitive ventricular endings nor afferent A fibers wer excited by PGI_2, PGE_2 or bradykinin. It was therefor postulated that stimulation of these chemosensitiv vagal afferent endings in the ventricle initiate refle bradycardia and hypotension produced by intracoro nary administration of prostaglandins and bradyki nin.[11,16–18] However, reflex hypotension and brady cardia after intracoronary injection of bradykinin wer observed only in dogs under barbiturate anesthe sia,[69,70] which depresses sympathetic nervous activity.[7] In dogs lightly[52] or fully anesthetized with chlo ralose,[28,72] intracoronary injection of bradykinin ma cause either pressor, depressor or biphasic changes i blood pressure that are always accompanied by tachy cardia. Hypotension associated with tachycardia is als produced by intracoronary or intravenous administra tion of PGE_2.[67,68]

A phenomenon of "sensitization," that is, an enhanced responsiveness on repeated stimulation, has been attributed to a decrease in the excitation threshold of polymodal sensory receptors associated with afferent C fibers.[73] Although the original concept was based on studies with polymodal (the term indicating that the receptors are excited by both mechanical and chemical stimuli) cutaneous nociceptors,[73,74] the phenomenon of sensitization, which involves a chemical intermediary,[73] may also apply to polymodal sensory nerve endings in the heart. Lombardi et al[75] drew attention to the ability of bradykinin to stimulate mechanosensitive sympathetic afferent endings in the heart, as well as a vast population of somatic C fiber afferent receptors in the skin and skeletal muscles, which are all polymodal. On the other hand, the stimulatory action of bradykinin on sensory nerves is associated with its ability to enhance prostaglandin production.[76,77]

Of the 3 types of vagal sensory receptors in the heart, only mechanosensitive endings with C afferent fibers, which innervate predominantly the left ventricle, may be regarded as polymodal since they are equally susceptible to mechanical stimulation by changes in ventricular volume and pressure or contractility, and to chemical stimulation with substances like nicotine.[13] These vagal afferent endings are also activated after acute coronary occlusion, probably as a result of increased end-diastolic ventricular pressure,[78] and are thought to be responsible for the reflex vasodilatation associated with myocardial ischemia.[79]

Sleight[15] observed a decrease in arterial pressure and bradycardia after intrapericardial or intracoronary injection of 50 to 100 μg of nicotine in dogs. Similar re-

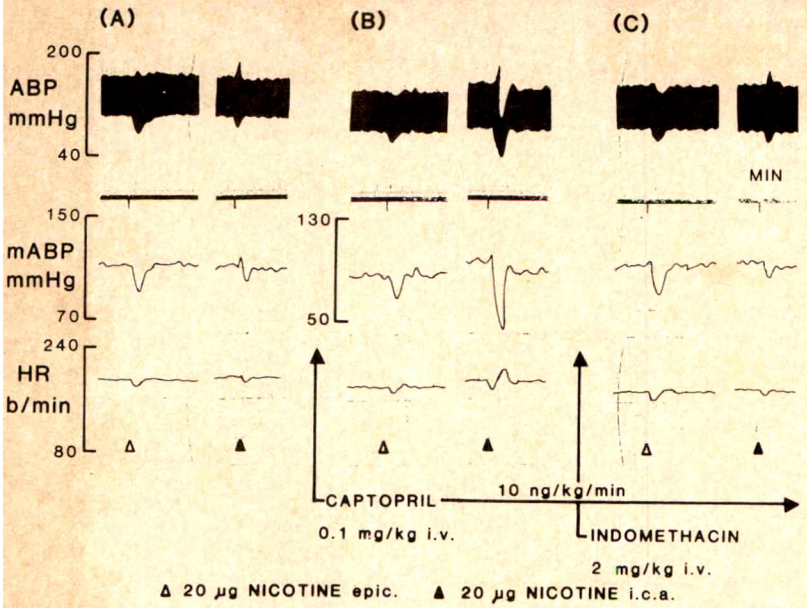

FIGURE 1. Pulsatile blood pressure (ABP), mean arterial pressure (mABP) and heart rate (HR) from an anesthetized, open-chest dog. Reflex hypotensive effects and bradycardia are induced with 20 μg of nicotine applied either to the surface of the left ventricle (**open triangles**) or injected into the left anterior coronary artery (**closed triangles**) under control conditions (**A**) and during treatment with captopril alone (**B**) and after intravenous administration of indomethacin (**C**). Treatment with captopril greatly enhanced the hypotensive response to intracoronary injection of nicotine, and this potentiating effect was completely abolished after indomethacin. Time scale is in minutes.

sponses occurred in our experiments in dogs with epicardial or intracoronary administration of 10 to 50 μg of nicotine. Our early investigations have shown that in contrast to the sympathetic pressor reflex evoked by epicardial application of bradykinin, the depressor vagal reflex induced by epicardial application of nicotine was not affected by treatment with indomethacin or by topical application of PGE_1 and PGE_2.[28] In subsequent studies,[64–66] topical application of PGI_2 (0.1 to 0.3 μg/min) and intracoronary infusion of PGE_2 (0.1 to 0.3 μg/min) also failed to influence the depressor and bradycardic responses induced by nicotine. However, a significant increase in the magnitude of the nicotine-induced reflex hypotension and bradycardia occurred during intracoronary or intravenous infusion of subdepressor doses (0.1 to 0.3 μg/min and 5 to 20 ng/kg/min, respectively) of PGI_2. Moreover, in several dogs that initially failed to respond to nicotine with reflex hypotension and bradycardia, these responses could be elicited during intravenous infusion of PGI_2.

It was still unclear, however, why the reflex effects of nicotine, unlike those of bradykinin, were not affected

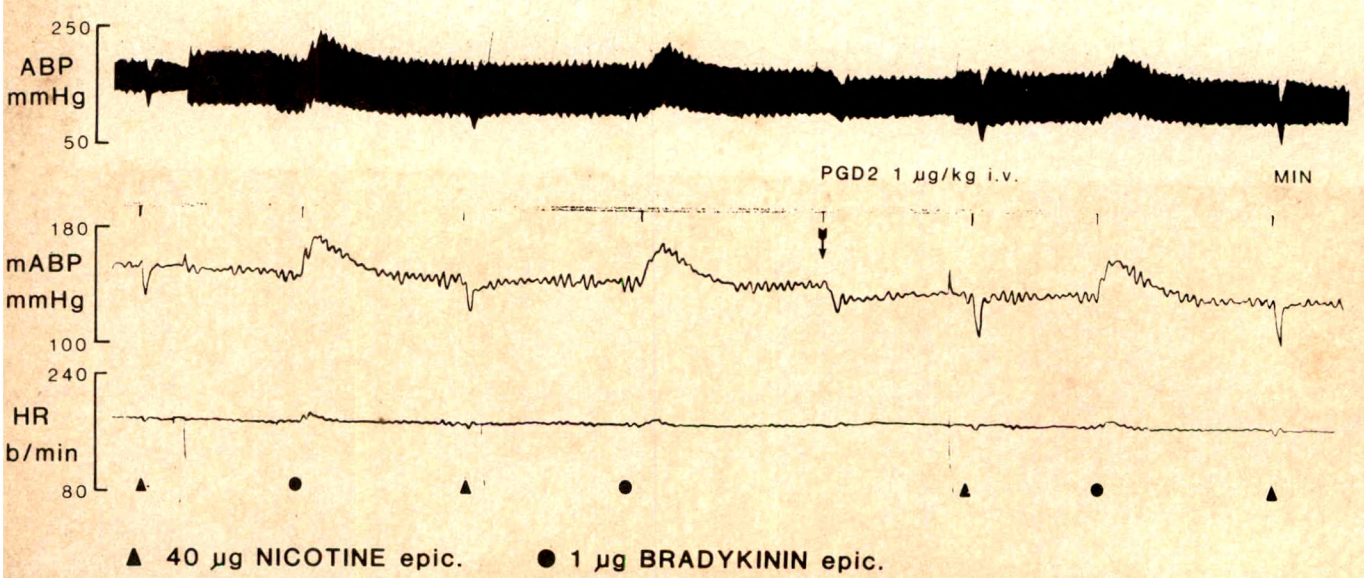

FIGURE 2. Potentiation of reflex depressor effects of nicotine after intravenous injection of prostaglandin D_2 (PGD_2). Records of pulsatile (ABP) and mean arterial pressure (mABP) and heart rate (HR) from a dog show responses produced by topical application to the left ventricle of 40 μg of nicotine (**triangles**) and 1 μg of bradykinin (**circles**) before and after intravenous injection of 1 μg/kg of PGD_2 (**arrow**). Injection of PGD_2 produced a decrease in blood pressure that was closely followed by a small increase in heart rate. After PGD_2, the magnitude of pressor and tachycardic response to bradykinin was not changed, but the hypotensive and bradycardic effects evoked by epicardial application of nicotine almost doubled. Time scale is in minutes.

by indomethacin. Some insight into this question was provided by the results of our recent investigations with captopril.[72] Captopril is an inhibitor of carboxy-dipeptidase, which functions as the angiotensin-converting enzyme and also as the major bradykinin-inactivating enzyme kininase II.[80] Consequently, treatment with captopril inhibits the formation of angiotensin II and at the same time enhances plasma level of kinins and potentiates vasodilator and other pharmacologic effects of exogenous bradykinin.[55,76] Bradykinin activates phospholipase A_2 and thus increases the availability of arachidonic acid for generation of various prostanoids,[81] which in turn contribute to vasodilator and other effects of bradykinin.[76] Observations that a decrease in blood pressure produced by captopril was reduced after indomethacin treatment suggested that the hypotensive effect was, at least in part, due to an increased release of prostaglandins.[82] Clough et al[83] reported that a decrease in blood pressure produced by captopril is not accompanied by a baroreflex-mediated increase in heart rate.[83] Our investigations with captopril[72] indicated that an enhanced reflex activity of vagal afferent receptors in the left ventricle, mediated by a prostaglandin mechanism, may contribute to the lack of effect on heart rate observed with captopril. Treatment with captopril greatly enhanced the magnitude of reflex depressor effects evoked by intracoronary administration of nicotine, and this potentiation was completely abolished by indomethacin (Fig. 1). These results clearly indicated that endogenous prostaglandins can sensitize polymodal vagal afferent endings in the ventricle and thereby enhance reflex depressor effects resulting from chemical or mechanical stimulation of these receptors. The sensitizing effect was probably due to an enhanced release of PGI_2 into the coronary or systemic circulation, since potentiation was particularly pronounced with intracoronary rather than with epicardial application of nicotine, and since PGI_2, but not PGE_2, potentiated the reflex effects of nicotine when infused in low doses into the coronary artery or intravenously.[64,65]

Recently, Hemker and Aiken[84] observed that the hypotension produced by intraarterial or intravenous injections of PGD_2 in cats was accompanied by bradycardia rather than tachycardia. Since bradycardia was blocked by treatment with atropine, it was suggested that PGD_2 activated vagal pathways. Our preliminary investigations with PGD_2 have shown that in anesthetized dogs, intravenous injections of 1 μg/kg of PGD_2 usually produce a small hypotensive effect associated with an increase in heart rate. However, in 4 of 6 dogs, we found a marked potentiation of the reflex hypotensive and bradycardic responses to epicardial or intracoronary nicotine, after intravenous injection of 1 μg/kg of PGD_2. A tracing from an experiment illustrating this effect is shown in Figure 2. The potentiating effect was usually prolonged, lasting for up to 30 minutes. In some experiments, further increases in the magnitude of nicotine-induced responses could be produced by an intravenous infusion of PGD_2 at a rate of 25 to 50 ng/kg/min. Surprisingly, no consistent potentiation could be obtained with intracoronary injections (0.3 to 1 μg/kg) or infusions (0.3 to 1 μg/min) of PGD_2, even though injections frequently evoked a decrease in blood pressure associated with bradycardia.

Recent investigations indicate that PGD_2 is formed in the blood and, like PGI_2,[85] is not inactivated during the passage through the lung; hence, it functions as a circulating hormone.[86] Our observations that intravenous PGD_2 enhances reflex effects of nicotine suggest that blood-borne PGD_2 may contribute to activation of vagal cardiac reflexes. However, the mechanism of the potentiating action of PGD_2 requires further investigation.

Role of Prostanoids in Regulation of Cardiac Reflex Activity and Coronary Resistance During Myocardial Ischemia: A Working Hypothesis

In 1976, Needleman[87] proposed a working hypothesis to account for the role of bradykinin and prostaglandins in modulating coronary resistance and cardiac reflexes associated with regional myocardial ischemia. According to this hypothesis, bradykinin released in the heart in response to ischemia promotes synthesis of PGE_2, and these 2 substances, acting independently or together, produce coronary dilatation and initiate cardiac chemoreflexes. As a result, coronary dilatation increases the oxygen supply, whereas reflex bradycardia decreases oxygen demand, thereby reducing the ischemia. In addition, the initiation of the pain sensation serves as the signal of an inappropriate stimulus to the heart that must be withdrawn.

It is now well established that coronary arteries are dilated by PGI_2 and contracted by PGE_2.[61,88] Furthermore, PGI_2, but not PGE_2, can induce[67,68] or potentiate[64,65] cardiac reflexes of vagal origin when administered into the coronary or systemic circulation. PGI_2 and not PGE_2 is a predominant active metabolite or arachidonic acid in blood vessels, including coronary vasculature.[61,89,90] Arachidonic acid is transformed into PGI_2 on passage through the lungs in vivo, whereas PGE_2 cannot be detected in arterial blood during infusion of the precursor fatty acid.[91] Furthermore, PGI_2 is only partially inactivated in 1 complete passage around the circulation,[85] a finding that reinforces the concept[92] that PGI_2 can function as a circulating hormone. However, Gryglewski[93] reported that there is a strong reduction in PGI_2 formation by hearts or vessels of rabbits made atherosclerotic. Similarly, there have been reports that human atherosclerotic tissue does not produce PGI_2, whereas tissue obtained from a nearby normal vessel does.[94] Patients with ischemic heart disease also have significantly lower levels of PGI_2 in the circulation, as well as lower capacities to generate and release PGI_2 in response to various stimuli (including ischemia) compared with healthy subjects who are the same age.[95] On the basis of these and other findings, Gryglewski[93] advanced a hypothesis that atherosclerosis is a disease from a deficiency of PGI_2 due to inhibition of PGI_2 synthetase by lipid peroxides or corresponding free radicals generated during hyperlipidemia.

PGI_2 is not only a vasodilator substance, but also a potent inhibitor of platelet aggregation in vitro and in vivo.[61,96–98] Aiken et al[98] showed that intravenous infusion of low doses of PGI_2 can prevent or reverse

thrombus formation in partially obstructed coronary arteries in dogs. On the basis of these and other observations, Moncada and Vane[61,96,97] suggested that PGI_2 or its chemical analogs could be used as a "hormone replacement" therapy in conditions in which excessive platelet aggregation is involved, such as acute myocardial infarction or crescendo angina.

Recently, therapeutic potential of PGI_2 was evaluated in patients with proved coronary artery disease. Bergman et al[99] reported that intravenous infusion of PGI_2 at rates of 2 to 8 ng/kg/min significantly reduced coronary vascular resistance and platelet aggregation induced with adenosine diphosphate. These effects on platelets and coronary resistance were accompanied by a prolongation of mean atrial pacing time to produce angina. Of particular interest, however, were observations reported by Szczeklik et al.[100] They found that low doses of PGI_2 (5 or 10 ng/kg/min) infused intravenously for 72 hours to patients with an ischemic heart disease completely abolished or significantly reduced a recurrence of attacks of spontaneous angina. However, anginal attacks precipitated by atrial pacing were not influenced by PGI_2 treatment. Since reductions in coronary vascular resistance and platelet aggregability were unlikely to be different in patients with spontaneous and pacing-induced angina (these were not measured), other actions of PGI_2, such as its ability to potentiate the effects of vagal stimulation in the heart, should be considered. Our experiments showed t small increments of PGI_2 in the circulation not c enhanced reflex effects of vagal origin, but also redu sympathetically mediated pressor responses evo with bradykinin.[64,65] There is also evidence for the istence of a cardiocardiac, vagosympathetic nega feedback reflex which can be initiated by sympath cally mediated increases in ventricular contractility. Increases in blood pressure and heart rate, which be attributed to reflex activation of sympathetic car and peripheral nervous activity,[3,25,28] frequently p cede the onset of pain in spontaneous angina.[2,41]

The effects of sympathetic stimulation may counteracted by activation of a vagosympath negative feedback mechanism, which can, in turn, amplified by sensitizing action of PGI_2 on mecha sensitive afferent nerve endings in the heart. T mechanism is unlikely to have a role in buffering effects of direct sympathetic stimulation imposed pacing. This may explain the effectiveness of PGI suppressing the attacks of spontaneous, but not p ing-induced, angina that Szczeklik et al observed.[1]

A working hypothesis that evolved from recent perimental and clinical findings is presented in Fig 3. It is postulated that a sudden oxygen deficit, prec itated either by an increased work load or a local va spasm superimposed on coronary atherosclerosis, result in regional myocardial ischemia. Once ischer

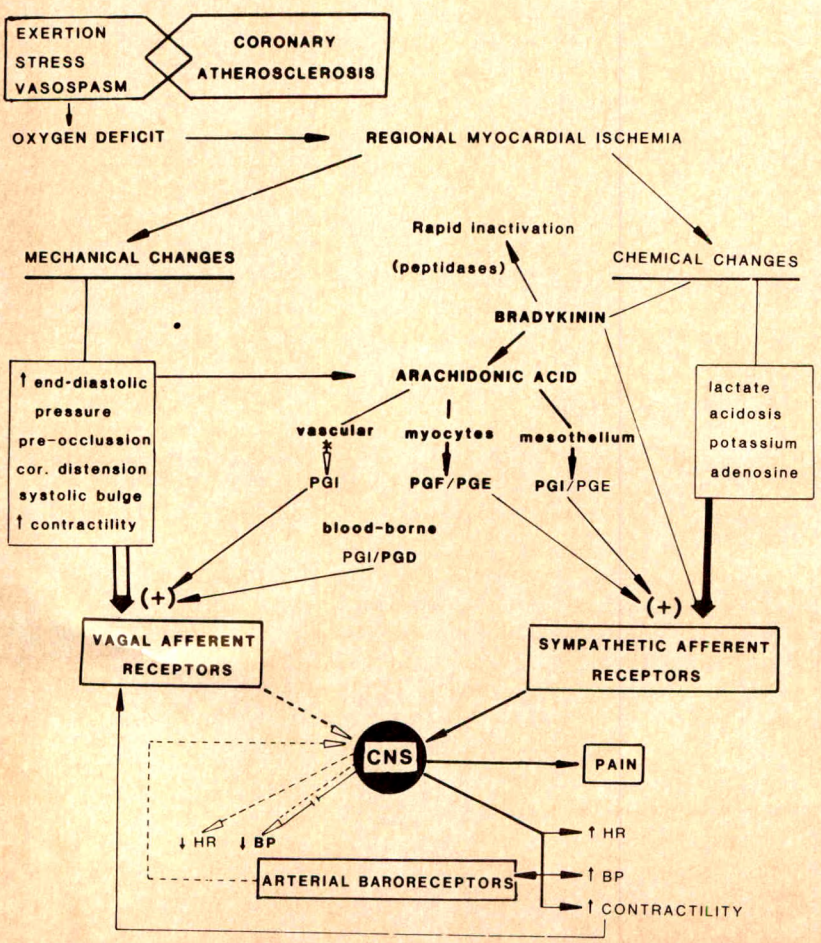

FIGURE 3. The events initiated by acute regional m cardial ischemia and their relative contribution to a vation of inhibitory and excitatory cardiovascular reflex BP = blood pressure; CNS = central nervous system; = heart rate.

occurs, mechanical and chemical changes are set in motion. A shift from aerobic to anaerobic metabolism leads to accumulation of lactic acid and local acidosis, which in turn can promote the release of potassium and adenosine and also activate kallikrein to form bradykinin. Concurrently, mechanical changes in left ventricular function and compliance with a subsequent increase in the end-diastolic ventricular pressure develop. These mechanical events, and particularly stretching and shortening of the bulging ischemic myocardium, can stimulate the release of arachidonic acid and increase generation of PGE_2 and $PGF_{2\alpha}$ by cardiac myocytes. Systolic bulging may also mechanically stimulate the pericardium to release PGI_2 and PGE_2 into pericardial fluid. On the other hand, distention of the coronary artery above the occlusion can stimulate PGI_2 synthesis by the residual healthy vascular endothelium. The synthesis of prostaglandins by various cell constituents of the heart and the pericardium can be further amplified by the release of arachidonic acid by bradykinin.

Except for the chemosensitive endings, activation of vagal afferent receptors in the ventricle can be attributed to mechanical stimulation. Activation of sympathetic afferent endings, on the other hand, may result predominantly from direct excitation by endogenous chemical substances acting in concert. Contribution of bradykinin to direct excitation may be restricted by its rapid inactivation by peptidases. However, by enhancing prostaglandin production, bradykinin can indirectly influence the sensitivity of vagal afferent endings to mechanical stimulation, and of sympathetic receptors to chemical stimulation by less potent but more stable substances such as lactate and potassium ions.

PGE_2 released from cardiac myocytes, together with PGI_2 deriving from epicardial and pericardial mesothelium, can sensitize sympathetic afferent receptors and thereby contribute to signaling of pain and to sympathetically mediated increases in blood pressure and cardiac rate and contractility. PGI_2 released into the coronary or systemic circulation could stimulate chemosensitive and sensitize mechanosensitive vagal receptors with C-fiber endings and, hence, contribute to reflex reductions in arterial pressure and heart rate. However, since PGI_2 synthesis by vascular endothelium is greatly reduced during atherosclerosis, this mechanism is unlikely to operate during ischemic heart disease unless this defect is corrected by administration of exogenous PGI_2. In the absence of PGI_2, blood-borne PGD_2 might contribute to activation of vagal afferent input from the heart. Of more importance in buffering the reflex effects of sympathetic stimulation may be activation of a negative feedback system through potentiation of cardiac vagal afferent activity by sympathetically mediated increases in ventricular contractility on the one hand, and activation of an inhibitory input from arterial baroreceptors on the other.

How the 2 inhibitory medullary inputs and the excitatory spinal input are connected and interact at the central level is not clear. On the output side, however, an amplified cardiac vagal efferent activity would tend to reduce cardiac rate and contractility, whereas reflex inhibition of sympathetic vasoconstrictor activity, together with stimulation of cholinergic sympathetic activity, would tend to reduce peripheral resistance and, consequently, blood pressure. These reflexly mediated mechanisms would reduce cardiac work and hence oxygen demand by the heart. Concurrently with reflexly mediated events, vasodilator metabolites such as adenosine[47] and, possibly, bradykinin,[87] would act to increase the oxygen supply. PGI_2 released from the residual healthy coronary endothelium or mesenchymal cells or both may contribute to coronary dilatation and at the same time reduce or reverse thrombus formation, increasing the patency of the vessel supplying blood to the ischemic area. All of the reflexly mediated and local mechanisms acting in concert may be responsible for the termination of an anginal attack uncomplicated by severe rhythm disturbances or circulatory collapse.

The present hypothesis incorporates in 1 framework a number of relevant, but hitherto unrelated, data on reflex and local changes occurring during regional ischemia resulting from obstruction of blood flow in the left anterior coronary artery. Acute ischemia of the posterior wall may trigger different reflex mechanisms[5] that were not considered in the present hypothesis.

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Variable Susceptibility to Dynamic Coronary Obstruction: An Elusive Link Between Coronary Atherosclerosis and Angina Pectoris

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Growing evidence suggests that dynamic coronary obstructions play an important but elusive role in the genesis of ischemic events. Dynamic coronary obstructions can develop during certain phases of coronary disease as a result of a variable combination of vasoconstriction, arterial wall lesions, and increased thrombotic tendency. In a certain phase of their disease some patients develop dynamic coronary obstruction, while others with a similar degree of fixed atherosclerotic obstruction do not.

Myocardial infarction and sudden death are much more likely to occur in angina pectoris of recent onset and during the waxing of symptoms than in the stable phases. If patients are to be managed rationally, it is important to know whether the onset and spontaneous variability of angina is caused predominantly by the progression of atherosclerotic coronary obstructions or by dynamic events that only transiently interfere with regional myocardial oxygen supply.

The investigators who specifically addressed themselves to this question favor the second hypothesis for most patients. Angiographic studies show that the severity of coronary atherosclerotic lesions is similar in stable and unstable angina.[1–3] Further, the waning of symptoms is not associated with detectable development of collateral vessels.[4] Continuous hemodynamic monitoring[5–9] and pacing tests[4,10] showed that attacks at rest are not caused by an excessive increase of myocardial demand. The disparate coronary artery findings in patients with electrocardiographically documented angina at rest[11,12] and, in particular, the recurring observation that about 10% of them have no detectable coronary stenosis[13,14] lend support to the hypothesis that transient coronary obstructions caused by smooth muscle contraction or by transient intraluminal plugging by blood constituents, rather than the severity of atherosclerotic obstructions by itself, are the common denominator of the onset of angina and a sudden worsening of symptoms.

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Dynamic stenosis occurs in some patients but not in others with comparable severity of atherosclerotic obstructions. Even in the same patient, there is variability from severe angina to improvement and even disappearance of pain for variable periods. These transient coronary obstructions are an elusive link between coronary atherosclerosis and clinical manifestations of ischemic heart disease. They are detectable at the very moment acute events take place, but not in routine angiograms or in postmortem studies. Together with the severity of fixed atherosclerotic coronary obstructions and with the impairment of contractile function, they determine both the symptoms and prognosis of ischemic heart disease.

In this report, we discuss the possible mechanisms of transient coronary obstructions, the relation between the dynamic factors and fixed atherosclerotic plaques, and their clinical implications.

The Turning Point

The major advance in our understanding of ischemic heart disease in the 1970s was the demonstration that decreased myocardial demand was not the only cause of angina.[5–9] Other mechanisms that only transiently interfere with myocardial oxygen supply can cause acute myocardial ischemia in the presence of an extremely variable degree of coronary atherosclerosis.[15] The second important finding was the angiographic observations of transient obstruction or critical narrowing of apparently normal as well as of atheromatous epicardial coronary arteries during spontaneous anginal episodes,[16] and the progressive reduction in the incidence of total coronary occlusion in the immediate hours and days after acute infarction, suggestive of early spontaneous recanalization.

Thus, routine angiographic studies performed when the patient is stable (and not during the acute episode) and postmortem examination may not necessarily reflect the state of the coronary arteries during acute events.

The problem is even more complicated in the patient with typical angina pectoris, usually exertional, who shows ischemic electrocardiographic changes, coronary sinus lactate production and pain during pacing, but has a normal coronary angiogram.[17] Such patients appear to have a reduced vasodilatory response to dipyridamole but no transient coronary obstruction. Thus, should this syndrome occur in patients who may have coronary plaques, one is tempted to attribute the cause of the ischemic episodes to these plaques without searching for other causes. The prevalence of the syndrome is unknown. Although clinically troublesome, it seems to have a good prognosis.

Fixed and Dynamic Coronary Artery Obstructions

Although either fixed or dynamic obstructions individually may be responsible for ischemic syndromes, their combination will have an enhanced influence on the symptoms and prognosis. A dynamic obstruction in a normal coronary tree is less likely to have devastating consequences than when there are multiple critical fixed obstructions. Conversely, even quite severe atherosclerotic narrowings may not cause symptoms if adequately compensated for by collaterals and if there is not an excessive increase of myocardial metabolic requirement. Under certain conditions, atherosclerotic plaques may, however, favor the development of dynamic obstructions.

Fixed Stenosis

An acute 85% diameter reduction of coronary lumen is required to reduce resting coronary flow.[18] Poststenotic pressure is reduced; this favors collateral flow. The number of collaterals and their response to pressure gradients may vary considerably among persons. Thus, the same degree of stenosis may limit considerably coronary flow reserve in patients with poor collateral development, but may be compensated for in others who have adequate collateral development, as in dogs. This difference in development of collaterals is best appreciated angiographically when the collaterals are large; it may be missed when they are small but numerous. If stenoses and collateral development were fixed, the impairment of coronary flow reserve should also be constant and ischemia would occur *only and every time* myocardial demand exceeds coronary flow reserve. Clinically, this situation should correspond to a rather fixed, predictable impairment of exercise tolerance and not to ischemia that occurs without detectable cause or at low levels of heart work.

Dynamic Stenoses

Dynamic stenoses are defined as changes in the caliber of epicardial coronary arteries that are transient, and therefore may not be detected postmortem or on routine angiography. We shall discuss the role of passive changes due to alterations in transmural pressure, of smooth muscle contraction, and of intravascular plugging.

Passive changes in vessel caliber: A recent series of studies[19,20] examined passive rather than active changes in caliber at the site of coronary stenosis in response to changes in transmural distending pressure. This mechanism, described by Burton[21] several years ago, predicts a decrease in lumen when transmural pressure is reduced and vessel closure when inflow pressure becomes lower than the critical closing pressure of the vessel. However, flow may not be influenced by the changes in lumen if the vessels are indeed collapsible.

In the absence of active tone, a reduction of outflow pressure (pressure at the venous side) in a collapsible vessel does not result in cessation of flow because a waterfall, or sluice, phenomenon takes place and the vessels behave like Starling resistors. Thus, the difference between inflow pressure and extravascular pressure at the site of the collapsible vessels becomes the driving pressure, and the level of outflow pressure becomes irrelevant as long as it is lower than extravascular pressure. In dogs with acute coronary stenosis produced with a snare to the point of preventing reactive hyperemia, a decrease in flow was observed after distal arteriolar dilatation.[22] We reproduced this phenomenon in carotid arteries of dogs without active tone only when the stenosis was produced by a snare: a decrease in flow was observed when distal pressure was reduced to low levels. The findings were opposite when comparable degrees of stenosis are produced by an intraluminal obstruction of similar degree (as it would be in the case of a subintimal plaque). We have shown that the difference in results was related to the inward protrusion of the intima caused by the snare, which is partially opposed by intraluminal pressure.[23] Also, isolated human coronary arteries with severe eccentric stenoses in the absence of active tone do not exhibit closure for levels of inflow pressure as low as 50 mm Hg, but they exhibit a waterfall phenomenon when outflow pressure is reduced. The presence of active tone will simulate, to a large extent, an increased extravascular pressure surrounding the collapsible segment. Therefore, vessel occlusion with interruption of distal flow can occur *only when smooth muscle tone results in a critical closing pressure higher than inflow pressure.* This appears unlikely unless tone increases.[24]

However, a passive wall collapse in an elastic coronary stenosis secondary to a decrease in distending pressure was recently postulated by Ganz[25] to explain vessel closure documented angiographically during spontaneous and exertional angina. This proposition appears untenable not only for the reasons discussed earlier, but also because if vascular occlusion were caused only by purely passive hydrodynamic phenomena, ischemic episodes should occur predictably every time perfusion pressure is lowered below a set level in any given patient. Nonetheless, during pacing-induced ischemia we could not find vessel occlusion in 10 consecutive patients (Fox KM, Davies GJ, Chierchia S, unpublished observations).

Coronary smooth muscle contraction: Coronary spasm has become an accepted cause of variant angina[26] and other ischemic syndromes.[27]

Recently, computerized measurements of coronary artery caliber on high-quality biplane angiography[28] have proved that at the site of severe organic narrowings, considerable coronary artery constriction can occur. This was seen during physiologic stimuli such as isometric exercise or cold pressor, and, conversely, considerable dilatation was produced by nitroglycerin. Thus, smooth muscle contraction in epicardial coronary arteries appears to be a cause of transient impairment of coronary blood supply.

As pointed out by Prinzmetal et al[29] and theoretically discussed by MacAlpin,[30] the increase of smooth muscle tone required to impair flow in a coronary artery branch could be small at the site of a subintimal plaque which already critically encroaches upon the lumen. Eccentric stenoses represent >70% of obstructions in coronary arteries, and they retain sufficient flexibility to be constricted by smooth muscle contraction.[31,32] Subintimal plaques can act as levers on the surrounding smooth muscle medial coat of the vessel so that even minimal changes in circumferential shortening can lead to a considerable reduction of the lumen. Conversely, the increase in smooth muscle tone must be considerable to impair flow in a normal segment of the vessel. On the basis of this consideration, MacAlpin suggested that normal changes in vasomotor tone may impair flow at the site of large subintimal plaques, whereas coronary spasm would more likely cause a reduction or impairment in the lumen in arteries without subintimal obstructions. On the basis of the present evidence we would, however, propose that both changes in vasomotor tone and spasm or abnormal changes in vasomotor tone can be responsible for vasoconstriction, but probably have different mechanisms.

Physiologic changes in vasomotor tone mainly control increases in flow across a stenosis at any given time and modulate the threshold for spasmogenic stimuli.[33] Increased vasomotor tone most likely contributes to the varying effort tolerance observed in patients in daily life, particularly in the cold or after meals, to the "walk-through" phenomenon, and to ischemia that occurs or worsens immediately after strenuous exercise.

We believe physiologic changes in vasomotor tone per se do not explain variant or spontaneous angina, because they are rare compared with the frequency of severe, obstructive plaques. These syndromes may occur only at certain times, and the constriction may not always occur at the site of the most severe atherosclerotic narrowing. Also, angiographic measurements during spasm do not support MacAlpin's hypothesis, because the calculated increase in tone is greater at the site of spasm than in other segments of the vessel.[34]

Coronary artery spasm may be caused by abnormal constrictive stimuli or by local supersensitivity to physiologic stimuli. These factors may explain the onset of spontaneous, unpredictable ischemic episodes more than passive changes in vessel lumen or physiologic changes in vasomotor tone alone for two reasons: (1) The spontaneous recurrence of angina interspersed with relative asymptomatic phases of the disease, so often observed in patients with angina at rest, suggest waxing and waning of some transient pathophysiologic mechanism. (2) Should passive changes in the lumen or increase in physiologic vasomotor tone play a major role per se, "spontaneous" angina should be much more frequent than is usually observed in patients with severe atherosclerotic narrowings. Although coronary artery diameter may decrease on the average by about 20% after ergonovine[35] or during handgrip exercise,[28] ergonovine is only positive in a minority of patients and only when they are in a hot phase of their disease,[36] independent of the severity of their organic coronary artery narrowings.

The mechanisms of coronary smooth muscle control are still speculative. Multiple receptors responsible for vasoconstriction have been identified in normal and in atherosclerotic segments of human coronary arteries.[37] Their role in the physiologic regulation of tone and in abnormal constriction is still poorly understood and is outside the scope of this report.

Thrombosis, thrombolysis, and platelet activation: The relationship between thrombus and myocardial infarction has been questioned on the basis of the extremely variable frequency with which postmortem studies showed a fresh occlusion in patients who died after myocardial infarction.[38] Postmortem studies represent a selection of large infarcts that are more likely to cause death and describe a static picture that may not reflect the situation at the very onset of myocardial infarction. Indeed, between the time of onset of infarction and that of the examination, thrombi can form or extend as well as undergo early lysis. Radiofibrinogen studies have indicated progressive late thrombus formation.[39,40] Conversely, angiography early after infarction showed complete vessel occlusion in 87% of cases within 4 hours of the onset of symptoms but in only 65% and in about 50% of cases when performed after 12 hours[41] and after 2 weeks,[42] respectively. The cause of occlusion and thrombus formation at a given moment in a given patient, which is the crux of the problem, remains speculative.

The mechanisms of occlusion in infarction might be related to those of spontaneous angina, because infarction is frequent in angina of recent onset or during worsening of symptoms. Also, it usually occurs in the same vascular territory that undergoes transient ischemia caused by transient spasm.[43–45]

Platelet aggregation was shown to cause transient complete vascular occlusion in dogs at the site of an acute, severe stenosis.[46,47] We observed at postmortem examination a mural thrombus composed of platelets and fibrin about 1 cm distal to the site of a complete occlusion that had been shown angiographically to be irreversible.[43] Platelet aggregation may be responsible for intraluminal plugging and may initiate thrombus formation, particularly when acute intimal damage is large, the balance between coagulation and lysis favors coagulation, and spasm is superimposed. Early lysis of thrombi or resolution of spasm, or both, can result in recanalization within a few hours or days; however, it may set the conditions for recurrent episodes of angina

pectoris caused by spasm or by transient intraluminal plugging.

Potential vicious circle: There may be a close interrelation between coronary smooth muscle constriction, intimal injury, and platelet activation and thrombosis. In normal arteries, intimal damage was documented after intense smooth muscle constriction.[48,49] In diseased arteries repeated or prolonged spasm under some circumstances may cause plaque rupture. The exposure of collagen elicits platelet activation and may initiate aggregation and thrombosis. Alternatively, platelet aggregation and thrombosis that forms because of a primitive intimal injury can result in intense coronary constriction because of the release of thromboxane A_2, serotonin and thrombin.

The repeated observation that in patients with variant angina, spasm usually occurs several times a day for long periods of time without causing permanent occlusion, and that disruption of plaques by transluminal angioplasty causes severe coronary spasm or thrombosis in only about 5% of cases, suggests the existence of protective mechanisms. Thus, a vicious circle can develop only when a set of unfavorable circumstances converge to favor intimal damage, thrombosis and smooth muscle contraction. This concurrence of unfavorable circumstances can be expected to take place only in some patients and only at a particular time, making them particularly susceptible to dynamic occlusion.

Variable susceptibility to dynamic obstructions: With the exception of angina in stationary phases, ischemic events are typically episodic. Isolated anginal attacks can occur occasionally, separated by months or years. Infarction can occur unheralded or preceded by few anginal attacks. Recent-onset angina or worsening periods begin unpredictably, sometimes rapidly culminating in infarction, but more often diminish and even disappear for months or years.[50–52] Waxing and waning periods are also common in stable exertional angina.

Should ischemic events occur as a consequence of a slow, progressive atherosclerotic narrowing, one might expect angina to appear for the first time during unusual increases of myocardial demand and, subsequently, progressively limit exercise tolerance. However, common clinical experience indicates that only occasionally does the first anginal attack occur during unusually heavy exertion; most often it occurs without apparent cause or during activities well tolerated both before and after the attack. Although it is often assumed that waning of symptoms is largely due to the development of collaterals, this possibility could not be substantiated by repeated arteriography in the study of Neill et al,[4] specifically designed to test the hypothesis.

There are several explanations as to why the individual susceptibility to dynamic obstruction may vary. First, a particular phase of the development of the atherosclerotic plaque may favor both smooth muscle contraction and intimal lesions. Second, abnormal vasoconstrictor stimuli or an increased vasomotor tone or both are most likely to occur occasionally. Finally, the increased thrombotic tendency that may favor an exaggerated response to intimal injury also seems to be transient.[53] As discussed before, these conditions may occur in 1 person but not in another, and may be present only during certain periods of life.

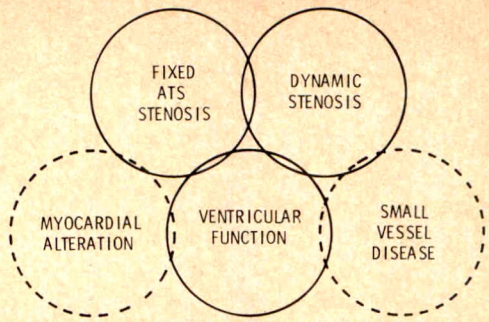

FIGURE 1. The possible determinants of prognosis and symptoms in ischemic heart disease. The major determinant of prognosis are ventricular function, the severity of fixed atherosclerotic lesions, and the susceptibility to dynamic stenoses. Hypothetical alterations of the small vessels and of myocardial metabolism may be responsible for angina but probably do not affect prognosis.

Clinical Implications

Symptoms and coronary atherosclerosis: The large variability in the relationship between severity of atherosclerotic coronary narrowings and symptoms may be explained to a considerable extent by 2 additional variables. On the 1 side, the individual response of collateral development for a given fixed stenosis conditions the severity of impairment of coronary flow reserve and, therefore, maximal exercise tolerance. On the other side, the variable susceptibility to dynamic stenosis conditions the appearance of ischemic episodes for levels of heart work, hence of myocardial oxygen requirement, which are well within the possibilities of the actual residual coronary flow reserve of the patient. This latter form of angina, also called "primary,"[54,55] may be caused also by mechanisms other than dynamic stenosis, namely by alterations of the small vessels or the myocardium or both (Fig. 1).

Determinants of prognosis: Although the relationship between severity of coronary stenosis and symptoms is quite variable, both elements appear to influence prognosis. In all published series the mortality at 5 years increases progressively with the number of diseased vessels found at arteriography, but mortality and infarction are higher among patients with unstable than with stable angina, in spite of no detectable differences in the severity of coronary atherosclerosis. We propose that this difference is largely related to the role of dynamic coronary stenoses. A greater susceptibility to dynamic stenoses could account, at least in part, for the mortality rate reported for patients with good ventricular function by Bruschke et al,[56] which was twice as high as that of the Coronary Artery Surgery Study[57] (Fig. 2). Patients referred to the Cleveland Clinic in the 1960s must have been much more symptomatic than those included in the CASS study (and not operated upon) in the 1970s. The 5-year mortality rate increases progressively with the degree of impairment of exercise

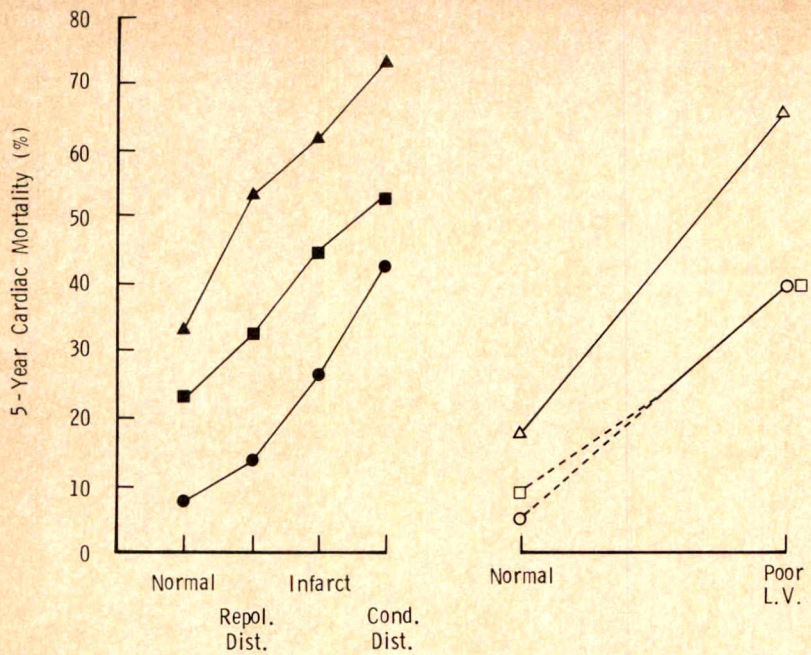

FIGURE 2. Five-year mortality in the series of Bruschke et al[56] (severely symptomatic patients, **closed symbols**) and in the Coronary Artery Surgery Study (CASS)[57] (nonoperated patients, **open symbols**). (**Circles,** 1-vessel disease; **squares,** 2-vessel disease; **triangles,** 3-vessel disease.) Although the mortality rate is similar in both studies for patients with poor left ventricular function, it is about one half in patients with normal ventricular function in the CASS study. Although the effects of changing medical therapy cannot be excluded, part of the difference may be that the patients in the series of Bruschke et al[56] were more symptomatic for comparable severity of coronary atherosclerosis because of greater susceptibility to dynamic obstructions.

tolerance assessed by stress testing[58]; we interpret this as a more severe fixed impairment of coronary flow reserve (resulting from the balance between severity of stenoses and development of collaterals).

Therefore, among patients with good ventricular function, it may become possible to identify subsets with an unfavorable prognosis because of poorer collateral development, greater susceptibility to dynamic obstructions, or both. The role of these prognostic determinants may be obscured by the presence of poor left ventricular function, which is, by itself, the major determinant of prognosis and was not appreciably different in the series of Bruschke et al[56] and in the Coronary Artery Surgery Study.[57]

Rational basis for therapy and prevention: Therapy of angina is still largely dominated by the primary aim of reducing myocardial oxygen requirements. The favorable response to beta blockers is used to validate this concept, but it is naive to assume that beta blockers have only this effect or that they act only through this mechanism. This attitude is reminiscent of that in the 1950s, when nitrates were thought to be effective because they increased myocardial blood flow. The hypothesis of an increase of myocardial demand exceeding coronary flow reserve was not supported by objective measurements, not only in patients with angina at rest but also for most episodes that occur during ambulatory monitoring of the electrocardiogram[59,60] in patients with stable angina. Thus, a *transient* impairment of myocardial oxygen supply may play a dominant role in angina. The role of dynamic stenosis in angina is beginning to be appreciated,[61,62] but it may have multiple mechanisms.[63] The identification of the role and varied mechanisms of dynamic stenoses help prevent anginal attacks caused by a transient impairment of flow rather than by an excessive increase of demand.

The prevention of dynamic stenoses and the assessment of coronary flow reserve by stress testing should help to identify the subset of patients who will benefit most from revascularization.

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Responses of Dog Large Coronary Arteries to Constrictor and Dilator Substances: Implications for the Cause and Treatment of Variant Angina Pectoris

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Canine circumflex coronary artery ring segments were mounted in organ baths and contracted by ergonovine (ergometrine), serotonin, phenylephrine, norepinephrine (in the presence of propranolol), potassium (K^+) and a thromboxane A_2 mimetic, U46619. Ergometrine was classified as a serotonin agonist since concentration-response curves were competitively inhibited by methysergide but not by alpha-adrenoceptor antagonists. Arteries precontracted to 80% of maximum were relaxed by verapamil, nifedipine and glyceryl trinitrate. However, nifedipine was 100-fold more potent against K^+ than either serotonin- or phenylephrine-contracted vessels. Verapamil showed some selectivity for K^+ and serotonin contractions compared with phenylephrine and was almost ineffective against U46619. Glyceryl trinitrate was without selectivity. Electrical field stimulation (2 and 20 Hz, 10-second) caused a weak contraction or relaxation or biphasic response in the isolated coronary ring. Contraction was amplified by propranolol (up to 1 μM) or metoprolol (50 ng/ml) and inhibited by alpha-adrenoceptor antagonists. In a blood-perfused left anterior descending coronary artery preparation, external diameter was measured by sonomicrometry under conditions of controlled flow and resistance. Intra-arterial serotonin, U46619 and ergometrine infusions decreased the diameter by up to 18% without causing spasm (0 lumen diameter). Lowering the perfusion pressure from 90 to 60 mm Hg increased the decrease in diameter during serotonin infusions. Verapamil (50 to 150 ng/ml) and nifedipine (15 to 45 ng/ml) inhibited, to a similar degree, the decrease in coronary artery diameter in response to serotonin infusions. However, verapamil was more effective than nifedipine in depressing the sinoatrial node, abolishing reflex tachycardia and lengthening the atrioventricular conduction time. These studies suggest that verapamil and nifedipine are only selective antagonists of constrictor agents in the dog coronary artery, that both low perfusion pressure and beta-adrenoceptor blockade may amplify constrictor responses, and that nifedipine has fewer cardiotoxic effects than verapamil.

Large coronary arteries decrease in luminal diameter by a maximum of about 20% during intravenous ergonovine (ergometrine) administration in man,[1] or methoxamine[2] or stellate ganglion stimulation in dogs.[3] This weak vasoconstriction of the large conduit vessels would not normally be sufficient to reduce coronary blood flow and induce angina. However, in some patients with Prinzmetal's variant angina,[4] the ergonovine provocative test may induce complete coronary artery occlusion (vasospasm), often at the site of a minimal organic lesion.[5,6] Although this clinical test is useful in demonstrating that spasm can occur, it does not necessarily help to identify the cause of vasospasm that occur spontaneously. At least 2 factors may be involved in vasospasm. First, a constrictor substance such as norepinephrine released from sympathetic nerve terminals, or serotonin or thromboxane A_2 released from platelets could initiate focal vasoconstriction. Second, this constrictor stimulus would require an amplifier before vasospasm occurs.

We investigated the reactivity of dog large coronary artery segments to sympathetic nerve stimulation and to a range of vasoconstrictor substances. Interactions of verapamil, nifedipine and glyceryl trinitrate with various vasoconstrictors were also assessed. Experiments were performed in isolated coronary artery ring segments in which changes in circumferential force were measured, and in a blood-perfused left anterior descending coronary artery (LAD) in which external diameter was measured by sonomicrometry. These 2 approaches have provided an insight into the variation of coronary constrictor agents in their requirement for extracellular calcium, suggested 2 factors other than fixed lesion that may amplify constrictor responses, and highlighted some differences in the cardiovascular properties of verapamil and nifedipine.

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Methods

Isolated coronary artery ring segments: Greyhound dogs (20 to 25 kg) of either sex were anesthetized with sodium pentobarbital (40 mg/kg, intravenously). The chest was opened and the heart removed. Approximately 4 cm of the proximal circumflex coronary artery was cleared of connective tissue and cut into 3-mm-long ring segments. The segments were suspended in a jacketed organ bath by 2 stainless-steel hooks; the lower hook connected directly to an isometric force displacement transducer (Grass FTO3C). The 30-ml organ baths contained a solution of a composition (in m*M*) of Na^+ 144, K^+ 5.9, Ca^{++} 2.5, Mg^{++} 1.2, Cl^- 128.7, HCO_3^- 25, SO_4^{--} 1.2, $H_2PO_4^-$ 1.2, and glucose II at 37°C, aerated with a gas mixture of 95% oxygen and 5% carbon dioxide. An initial force of 4 *g* was applied and readjusted to this level 30 minutes later if necessary. As many as 12 ring segments were cut from each circumflex artery and 6 rings were used concurrently.

After 60 minutes of equilibration, concentration-response curves were constructed by the cumulative addition (0.5 log unit increments) of constrictor substance until the maximal response was achieved. Alternatively, concentrations of verapamil or serotonin antagonists were left in contact with the tissue during the 60-minute equilibration period. In all experiments, only a single concentration-response curve with or without antagonist was obtained in each segment. The advantages of this design have been discussed previously.[7] In a second series of experiments, ring segments were constricted by a single concentration of agonist chosen to cause approximately 80% of the maximal response to that drug. When the constriction had reached a plateau, the ring segments were relaxed toward the preconstricted level by the cumulative addition of verapamil, nifedipine or glyceryl trinitrate.

Responses to sympathetic nerve stimulation were measured after square-wave monophasic electrical field pulses (2 or 20 Hz, 2 ms duration, 10 V/cm) (Grass SD9) for 10 seconds delivered from platinum field electrodes placed either side of the coronary ring segment. The field pulses were monitored on an oscilloscope. Only 2 periods of 2- and 20-Hz field stimulation were given to any 1 ring segment, the second period after 30-minute equilibration with propranolol, metoprolol or phentolamine. Some segments were pretreated with an irreversible alpha-adrenoceptor antagonist (benextramine) or propranolol before the first period of field stimulation.

Measurement of coronary artery diameter: A 5-cm length of LAD together with a 3-cm-wide portion of the surrounding myocardium was separated from a dog heart immediately after its removal from an anesthetized greyhound. The tissue was immersed in cold oxygenated Krebs' solution (see coronary ring method). The LAD was cannulated near its origin and again 3 to 4 cm distal. A small catheter was placed in a side branch of the LAD to monitor intraluminal perfusion pressure. Heparinized femoral arterial blood from an anesthetized support dog (pentobarbitone, 30 mg/kg intravenously and 6 mg/kg/h) was pumped (Watson-Marlow) through the coronary artery segment at 50 ml/min and then through a pneumatic Starling resistance before being returned to the femoral vein of the support dog (Fig. 1).

Continuous phasic external coronary artery diameter was measured by the transit-time ultrasound technique.[8] With minimal dissection, a small, lightweight piezoelectric receiver crystal (1.5 mm × 3 mm, 5.4 mg) was placed beneath the LAD. A second emitter crystal (9 MHz) of similar dimensions was glued to the upper surface of the LAD (directly above the receiver crystal) with a small amount of tissue adhesive (cyanoacrylate, Eastman Kodak 910). The accuracy, linearity and stability of the entire system resolves changes in diameter of <0.01 mm and does not drift over long periods.

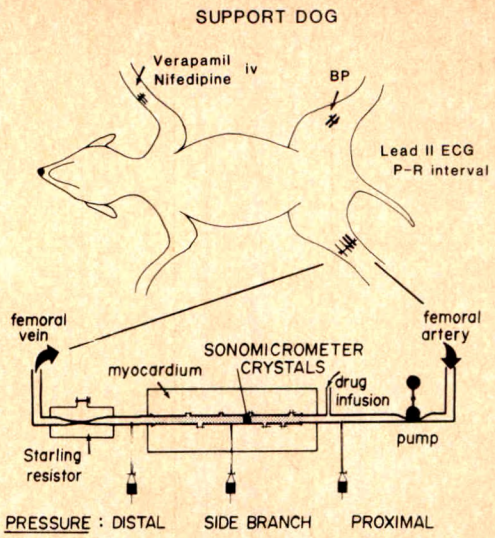

FIGURE 1. The in vivo experiments in which the arterial blood from a support dog was used to perfuse the left anterior descending coronary artery from another heart under conditions of controlled flow and resistance. BP = blood pressure.

The surrounding myocardium was clamped to limit the perfusion of the coronary resistance vessels as much as possible. When this perfusion did occur, the venous blood was collected in a polyethylene tray and returned to the supporting dog. Serotonin (or saline solution) was infused (at 1 ml/min by roller pump) directly into the coronary artery by a side-hole catheter in the proximal cannula. This procedure allowed cumulative concentration-response curves to be readily obtained by changing the concentration of the serotonin infusion in 10 ml vials. The proximal and distal perfusion pressures were monitored from side ports (Fig. 1). Mean and phasic LAD external diameters were continuously measured. Hemodynamic measurements from the support dog included aortic blood pressure from a catheter advanced from the femoral artery and heart rate and the PR interval from the lead II electrocardiogram run at 100 mm/s chart speed. During verapamil experiments, a bipolar pacing catheter (USCI-No. 6F) was inserted into the right ventricle through the external jugular vein. The effect of verapamil and nifedipine as vasodilators in the large coronary artery was evaluated by the degree of blockade of serotonin concentration-response curves. After the intracoronary infusion of serotonin, (±) verapamil was given by bolus and infusion intravenously to the support dog to increase the plasma level to 50, 150 and 500 mg/ml. The plasma levels were not measured, but were calculated from the first-order kinetics of verapamil in dogs.[9] The actual doses were 0.67, 1.56 and 4.47 mg/kg given slowly over 5 minutes, followed by infusions of 9.3, 31, and 93 μg/kg/min for 50, 150, and 500 ng/ml levels, respectively. After 10-minute infusion of each level of verapamil, the serotonin concentration-response curve was started. A similar protocol was followed for nifedipine except that only intravenous bolus injections were given to the support dog, since this drug has a long half-life compared with verapamil (150 to 180 versus 15 to 30 minutes).[10] Doses of nifedipine were 15, 45 and 150 μg/kg.

At the end of each experiment, a double-bladed scalpel was used to remove a 4.33-mm length of LAD taken from the area of the sonomicrometer crystals. From the weight of this segment (W) and the tissue density (1.06), the wall volume (Vw)

was calculated as Vw = W/1.06. The internal radius (Ri) was calculated from $Ri^2 = Re^2 - (Vw/II.L)$, where Re is the external radius.

Drugs were freshly prepared daily and diluted in distilled water. Drugs used were benextramine tetrahydrochloride, methysergide bimaleate, and pizotifen malate, (−) noradrenaline bitartrate dissolved in ascorbic acid, 0.1 n*M*, phenylephrine hydrochloride, cyproheptadine hydrochloride, (±) propranolol hydrochloride, prazosin hydrochloride, ergometrine maleate, serotonin creatinine sulphate, (±) verapamil, U46619 (15 S-hydroxy-9α,-11α-(epoxymethano) prosta-5Z 13E-dienoic acid) and glycerol trinitrate; nifedipine was dissolved in polyethylene glycol 300 and protected from light.

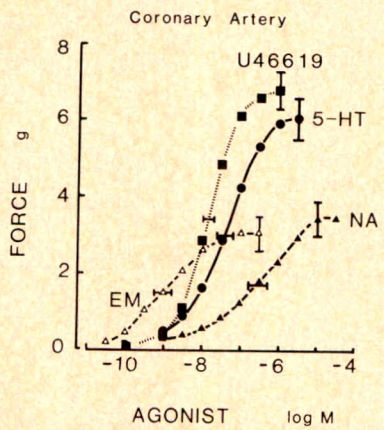

FIGURE 2. Comparison of the potency and magnitude of 4 constrictor substances in isolated coronary artery rings. Ordinate, change in isometric force (g); abscissa, concentration of constrictor (log units). EM = ergometrine; U46619 = thromboxane A_2 mimetic; 5-HT = serotonin; NA = norepinephrine in the presence of propranolol (1 μM). Error bars are ±1 standard error at maximal response or at EC_{50} (horizontal).

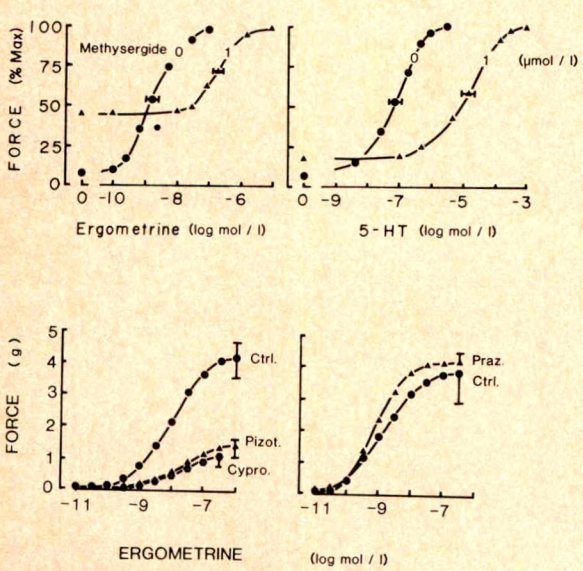

FIGURE 3. Concentration-response curves to ergometrine and serotonin (5-HT) in isolated coronary ring segments. **Top,** methysergide (1 μM) was a competitive antagonist of both ergometrine and 5-HT. **Bottom,** pizotifen (pizot) and cyproheptadine (cypro) (1 μM) were noncompetitive antagonists. Prazosin (pra), 10 n*M*, failed to antagonize ergometrine concentration-response curves. Error bars are ±1 standard error for 5 to 7 rings. ctrl = control.

Results

Isolated coronary ring segments: *Constrictor substances:* The most potent constrictor substance found on the circumflex coronary ring segment was ergonovine (ergometrine) (Fig. 2). However, the magnitude of the maximal response was substantially less than either serotonin (5HT) or a thromboxane A_2 mimetic drug, U44619. Norepinephrine in the presence of propranolol was similar (although less potent) to ergometrine in terms of magnitude. Phenylephrine, a more selective alpha-adrenoceptor agonist, was similar to norepinephrine.

The receptor mediating the response to ergometrine was classified as a serotonin receptor and not an alpha-adrenoceptor from the following observations.

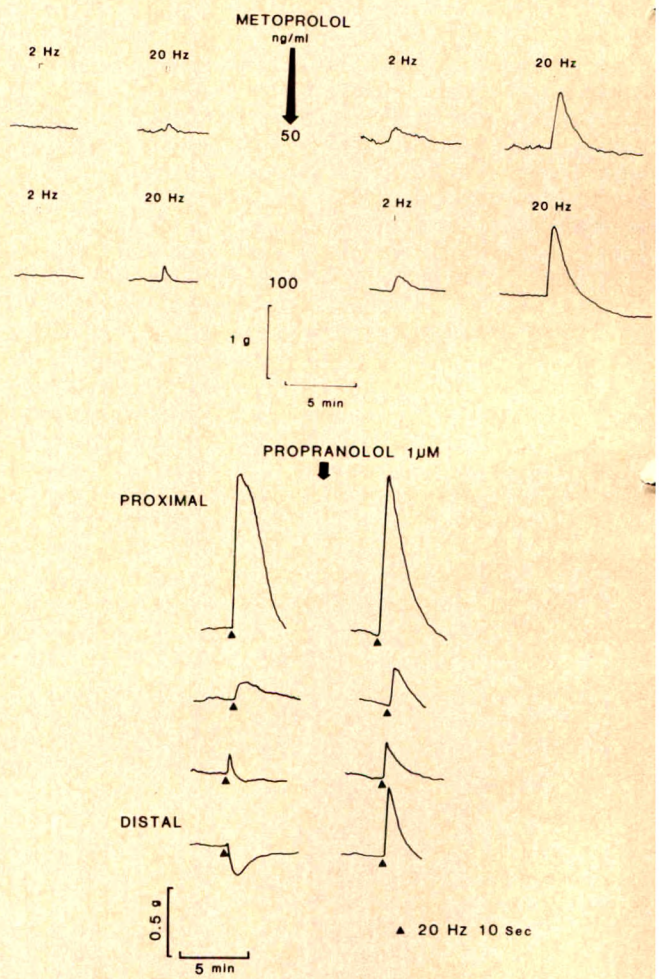

FIGURE 4. Traces from isolated coronary ring segments during electrical field stimulation (2 or 20 Hz, 10 seconds). **Top,** metoprolol experiments. Two rings from 1 circumflex coronary artery before (**left**) and in the presence (**right**) of metoprolol, 50 ng/ml (top ring) and 100 ng/ml (bottom ring). **Bottom,** traces from 4 rings from 1 circumflex coronary artery (15 mm long) arranged in order from proximal to distal, showing different responses to 20-Hz field stimulation. **Left,** control responses; **right,** in the presence of propranolol, 1 μM.

In guinea pig aorta, a tissue responsive to alpha-adrenoceptor stimulation, both ergometrine and serotonin were inactive (up to 1 μM). In dog coronary artery, the specific alpha-adrenoceptor antagonist prazosin, or the irreversible alpha-adrenoceptor antagonist benextramine, failed to block the response to ergometrine (Fig. 3). More precision was achieved with serotonin antagonists. Methysergide was the only antagonist that has been claimed to block serotonin receptors that displaced the ergometrine and serotonin concentration-response curves in parallel without reduction in maximum. The estimated dissociation constant (K_B) for methysergide was similar for ergometrine and serotonin as agonists (13 and 10.2 nM), indicating that ergometrine was a serotonin receptor agonist in this tissue.[11] Methysergide was also a constrictor substance itself in these experiments (partial agonist), as shown by the increase in baseline before the commencement of the agonist curves (Fig. 3). In contrast, other serotonin antagonists, pizotifen and cyproheptadine (1 μM), were noncompetitive antagonists of ergometrine without causing a constrictor response on their own (Fig. 3).

Sympathetic nerve stimulation: Ring segments cut from a single 3-cm length of circumflex coronary artery often responded differently to electrical field stimulation. Some segments contracted and others relaxed, but most showed a biphasic response pattern of early constriction followed by more prolonged relaxation (Fig. 4). The responses were mediated by norepinephrine released from sympathetic nerves, since a combination of propranolol (1 μM) and phentolamine (1 μM) completely abolished all responses as did the Na^+ channel blocker tetrodotoxin (0.1 to 1 μM). In segments pretreated with the irreversible alpha-adrenoceptor antagonist benextramine, only marked relaxation was observed to field stimulation, a response that was subsequently blocked by propranolol (Fig. 5). In arteries pretreated with propranolol (1 μM) or metoprolol (50 to 100 ng/ml, a concentration observed in the plasma of patients in treatment for exercise-induced angina), the constrictor response was enhanced (Fig. 4 and 5). These findings emphasize that large coronary arteries are neurally innervated and that responses may be mediated by alpha- or beta-adrenoceptors or both.

Vasodilator substances: In the isolated ring segments, the specificity of the dilator action of verapamil,

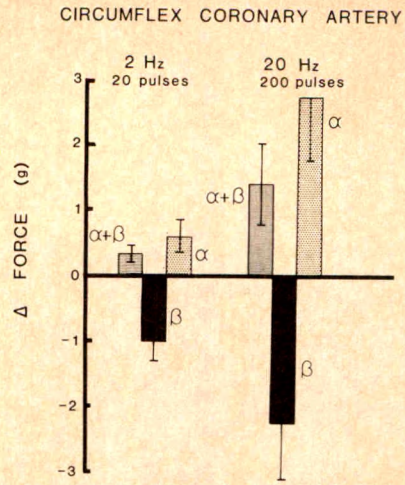

FIGURE 5. Group results for circumflex coronary artery ring segments to electrical field stimulation at 2 and 20 Hz for 10 seconds. Only 1 treatment was performed on each ring segment. Control (alpha- + beta-adrenoceptors), n = 7; benextramine 10 μM (beta-adrenoceptors only), n = 8; propranolol 1 μM (α-adrenoceptors only), n = 4. Error bars are ±1 standard error.

nifedipine and glyceryl trinitrate was compared in arteries contracted submaximally with K^+, (25 mM), serotonin (0.3 μM), phenylephrine (1 μM), and the thromboxane A_2 mimetic U44619 (0.03 μM). Glyceryl trinitrate relaxed the arteries with a similar IC_{50} value (concentration giving 50% inhibition of contraction) for each of the 4 constrictor agents (Fig. 6). In contrast, the slow calcium-channel blockers nifedipine and verapamil showed marked differences in their ability to relax arteries contracted by the 4 constrictor substances. Nifedipine was very potent against K^+ depolarized arteries ($IC_{50} = 8.5 \times 10^{-9} M$) but was relatively weak against both serotonin ($IC_{50} = 1.8 \times 10^{-6} M$) and phenylephrine ($IC_{50} = 1.7 \times 10^{-6} M$) contracted arteries. Verapamil was much weaker than nifedipine against K^+ ($IC_{50} = 1.1 \times 10^{-6} M$), but was similar against serotonin ($IC_{50} = 1.5 \times 10^{-6} M$). Verapamil was 4-fold more potent against serotonin-contracted tissues than against phenylephrine. However, in contrast to glyceryl trinitrate, verapamil was extremely ineffective against coronary rings contracted by U46619. This difference could not be accounted for by different absolute starting levels of constriction, since glyceryl trinitrate was equally ef-

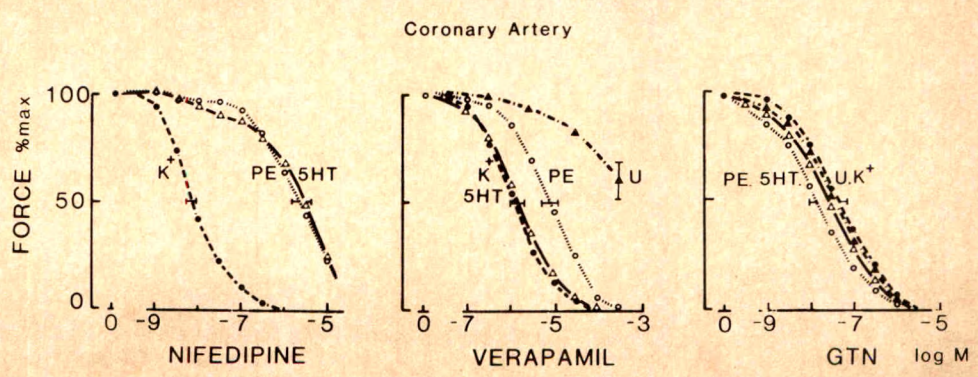

FIGURE 6. Relaxant effects of nifedipine, verapamil, and glyceryl trinitrate (GTN) in isolated coronary artery rings contracted by K^+ (25 mM), phenylephrine (PE, 1 μM), serotonin (5HT, 0.3 μM), or thromboxane A_2 mimetic (U46619, 0.03 μM). **Ordinate,** change in force, percentage of maximal response to constrictor agent; **abscissa,** concentration of dilator agent (log scale). Horizontal error bars are ±1 standard error at IC_{50} (concentration giving 50% inhibition of contraction) for ≥6 rings in each curve. Only 1 curve was obtained in each ring.

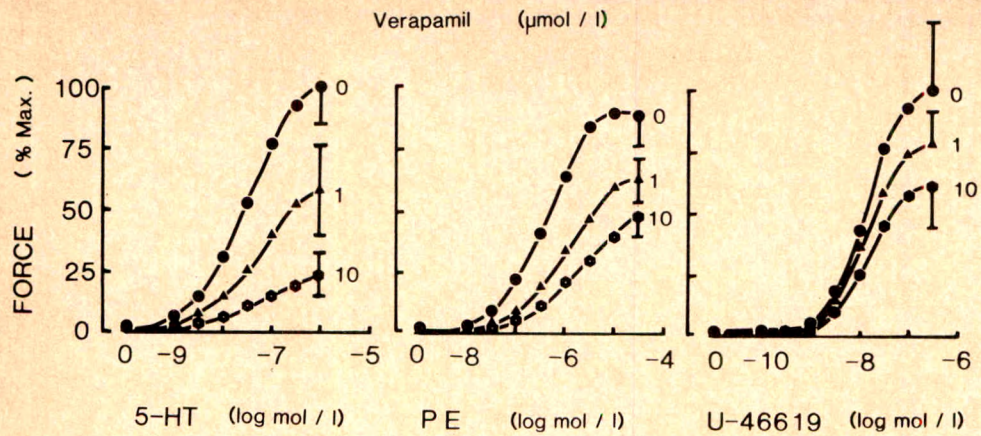

FIGURE 7. Effects of verapamil (0, 1 and 10 μM, 60-minute contact) on vasoconstrictor responses to serotonin (5-HT), phenylephrine (PE) and the thromboxane A_2 mimetic U46619 in isolated coronary ring segments. Only 1 concentration-response curve was obtained in each ring. Values are mean ±1 standard error, with at least 5 tissues per verapamil concentration.

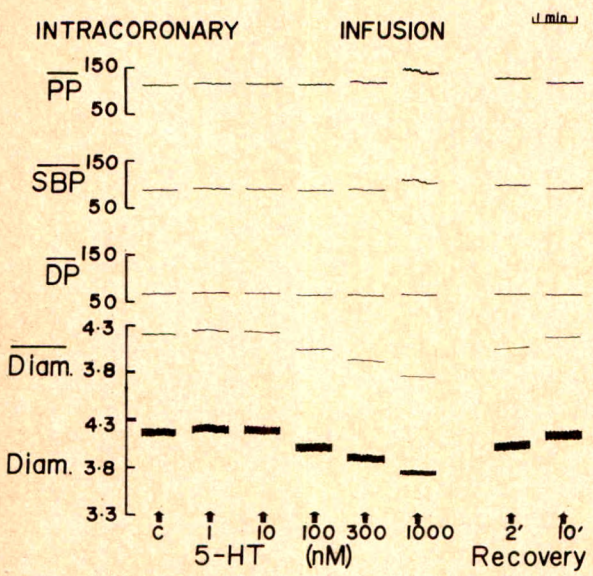

FIGURE 8. Hemodynamic measurements during intracoronary infusions of serotonin (5-HT). From top, the records are mean proximal perfusion pressure (PP), mean side branch pressure (SBP), mean distal pressure (DP), mean (DIAM) and phasic (DIAM) external coronary artery diameter. All units of pressure are in millimeters of mercury and diameter is in millimeters. Recovery traces are shown at right.

fective against the same concentration of constrictor agents.

In a different experimental design in which verapamil was equilibrated with the artery before the addition of the constrictor agent, a similar pattern was noted (Fig. 7); that is, verapamil (1, 10 μM) was more effective against serotonin concentration-response curves than against phenylephrine. The poor inhibition by verapamil of the response curve to U46619 may suggest that this constrictor does not require extracellular Ca^{++} for contraction. In 6 coronary rings equilibrated for 45 minutes in Ca^{++}-free Krebs' solution, serotonin and phenylephrine failed to elicit a contraction, while U46619 was still most effective (80% of normal).

Diameter measurements in situ: *Pressure-diameter relationship, serotonin, U46619, ergometrine:* The relationship of intraluminal pressure (measured from side branch in the LAD) to luminal diameter of the coronary artery was curvilinear, the artery showing greater passive changes in diameter in pressures from 50 to 100 mm Hg than from 100 to 150 mm Hg. In each preparation, the pressure/diameter type curve was determined by varying the pressure in the Starling resistor. Intracoronary serotonin infusions at a side branch pressure of 90 mm Hg lowered the external diameter, calculated internal diameter and area in a concentration-dependent manner (Fig. 8 and 9). The decrease in diameter was clearly an active response to the serotonin and was not due to a decrease in luminal pressure, emphasizing an advantage of this preparation in defining the magnitude of diameter change in large coronary vessels. The diameter returned rapidly to preinfusion levels when the serotonin was replaced by 0.9% sodium chloride. Serotonin infusions did not alter the hemodynamics in the support dog, presumably because the metabolism of serotonin through the lungs and dilution on entering the femoral vein. Intracoronary infusions of U46619 up to 1 μM caused a decrease in diameter similar to serotonin, but was approximately 3-fold more potent. At 0.3 and 1 μM, U46619 caused marked cardiovascular changes in the support dog including hypertension, tachycardia and an increase in central venous pressure. Ergometrine (1 to 1000 nM) caused a maximal decrease in luminal diameter of only 12%, about half that of serotonin. The recovery of diameter after stopping U46619 was approximately 30 minutes, and >1 hour after ergometrine. We never observed a decrease in luminal diameter of >40% for any of these constrictor substances.

Amplification of constriction: The effect of perfusion pressure on the magnitude of the decrease in diameter to serotonin infusions was examined. In each artery complete concentration-response curves to serotonin were obtained at 60 and 90 mm Hg intraluminal pressure. These pressures were set before the infusion of serotonin by adjustment to the Starling resistance. The diameter decreased to a lower level during serotonin infusions with 60 mm Hg perfusion pressure, principally because the starting diameter was lower than at 90 mm Hg (Fig. 9). No significant change was observed in the potency of serotonin.

Simple geometric considerations of the effect of luminal encroachment by 20 to 40% (as in atheromatous

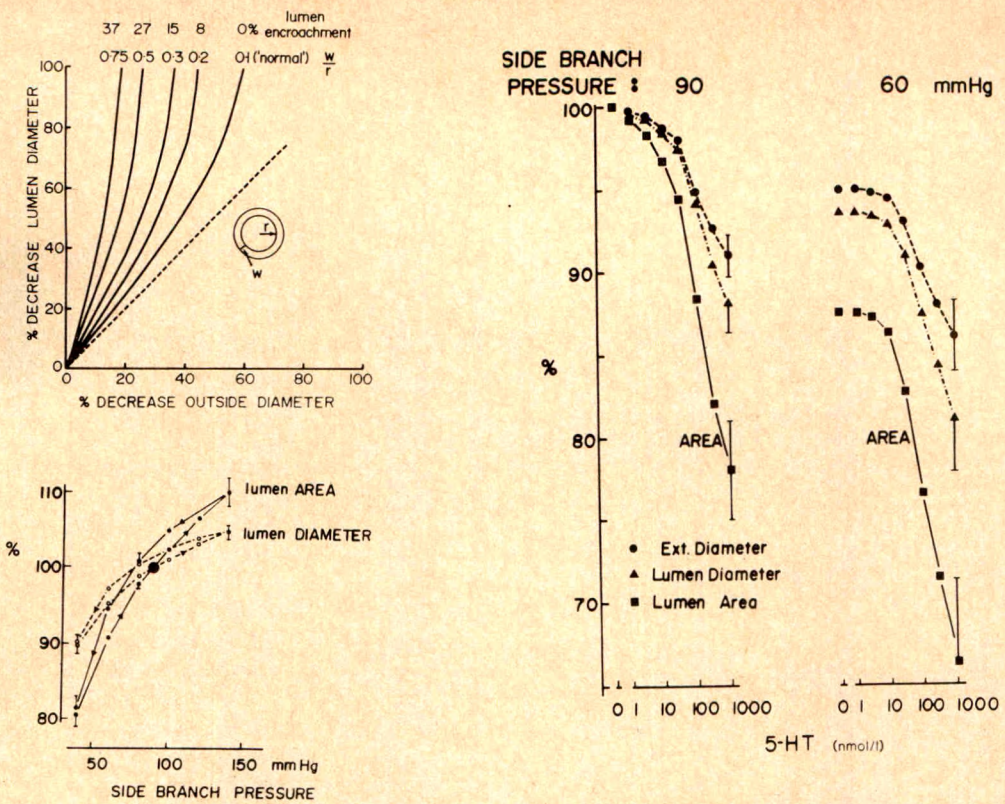

FIGURE 9. Left top, theoretical relation between percent changes in outside diameter and percent change in luminal diameter of a coronary artery when the ratio of wall thickness to lumen radius varies from 0.1 to 0.75. If the ratio of 0.1 is taken as a normal artery, the percent luminal encroachment at rest is calculated for the higher ratio. Adapted from MacAlpin.[33] **Left bottom,** effect of altering perfusion pressure on the luminal diameter and luminal area. Measurements were calculated as percentage of values at 90 mm Hg. **Right,** effect of perfusion pressure (90 mm Hg left, 60 mm Hg right) on the magnitude of decrease in coronary artery diameter during intracoronary serotonin (5-HT) infusions. External and internal diameter and luminal area were measured as percentage of value at 90 mm Hg before the start of the serotonin infusion. Values are mean ± standard error in 10 arteries. Both curves were completed in each artery.

lesions or by wall thickening) suggest that relatively small decreases in diameter (20%) should be sufficient to reduce the luminal diameter to almost 0 (Fig. 9).

Comparison of verapamil and nifedipine in vivo: Full serotonin concentration-response curves could be readily repeated up to 4 times in the blood-perfused LAD preparation. The maximal decrease in luminal area from preinfusion level was 20 to 25%. As the concentration was increased further, the diameter started to return toward control (Fig. 10). If the maximal decrease in luminal area for the first concentration-response curve to serotonin was considered to be 100%, the second and third curves repeated in the same artery were virtually identical in sensitivity and magnitude (Fig. 11). In support dogs without calcium-channel blocker, systemic blood pressure decreased gradually (by 19 mm Hg) over 5 hours, the period in which 4 serotonin-response curves were completed. The heart rate and PR interval remained steady throughout this period (Fig. 12). In contrast, both nifedipine and verapamil lowered blood pressure in a concentration-dependent fashion. Heart rate was elevated by nifedipine administration but was reduced substantially by verapamil (Fig. 12). Atrioventricular conduction was unaffected by the lower concentrations (15, 45 ng/ml) of nifedipine, whereas verapamil caused marked increase in PR interval even with the first concentration (50 ng/ml). With

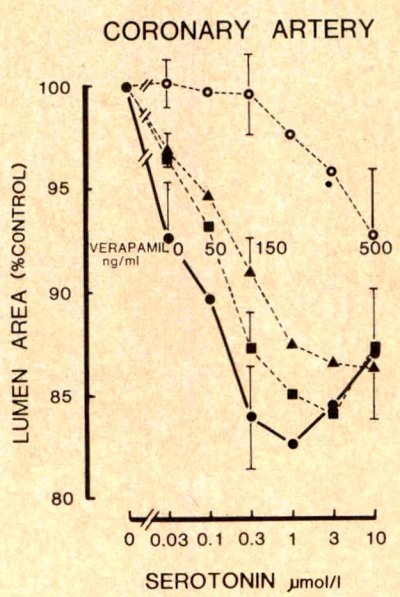

FIGURE 10. Effect of verapamil on constrictor responses to serotonin in blood-perfused left anterior descending coronary artery. Verapamil was given by intravenous bolus and infusion to the support dog to give plasma levels calculated to be 50, 150, and 500 ng/ml. Each artery (n = 8) had 0 and 50 ng/ml verapamil, but only 7 and 5 of these, respectively, had 150 and 500 ng/ml. Responses were calculated as luminal area, taking control values at the start of each serotonin curve as 100%.

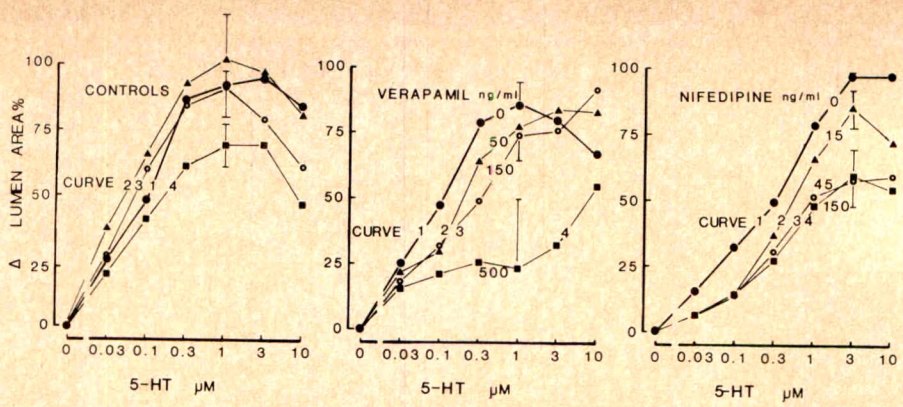

FIGURE 11. Effect of verapamil and nifedipine on constrictor responses to serotonin (5-HT) infusions in the perfused left anterior descending corona artery. **Ordinate,** decrease in luminal area as a percentage of the maximal decrease to serotonin observed in the first curve in each artery. Subsequ curves (2, 3, and 4) were obtained without antagonist (**left**), or in the presence of verapamil (50 to 500 ng/ml, **middle**) or nifedipine (15 to 150 ng/ **right**). Both antagonists were administered to the support dog. Error bars are ±1 standard error. Controls, n = 5; verapamil, n = 5 to 8; nifedipi n = 6.

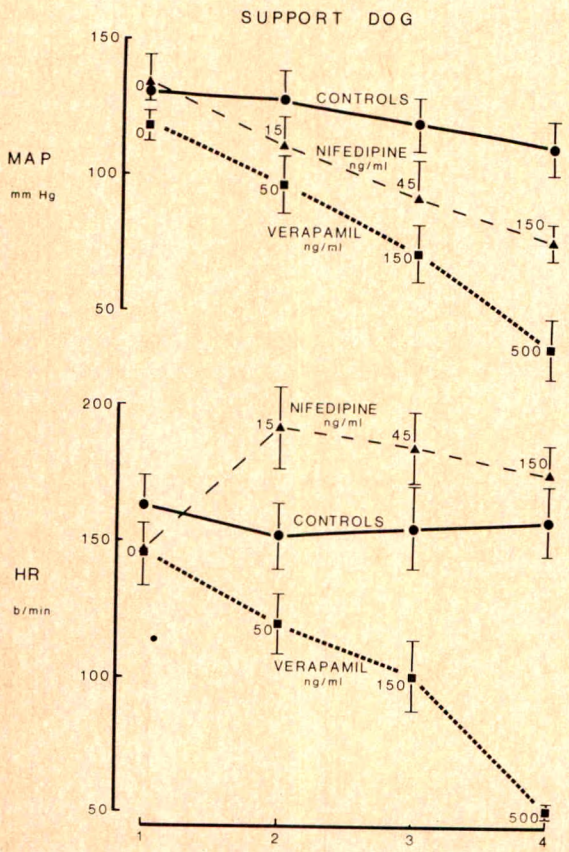

FIGURE 12. Mean arterial pressure (MAP) and heart rate (HR) values for the support dogs during the 4 serotonin infusions (numbers 1 to 4 on **abscissa**). There were 3 groups of dogs; control, **circles;** nifedipine, **triangles;** and verapamil, **squares.** The concentrations of calcium antagonists are shown. Error bars are ±1 standard error.

150 ng/ml of verapamil, 5 of 7 dogs had atrioventricular block (Fig. 13). The range of concentrations of both verapamil and nifedipine were closely matched in their ability to reduce the coronary constrictor response to serotonin (Fig. 11). With the lower concentrations of verapamil (curve 2 and 3), the decrease in diamet during serotonin infusions was less than that during t control curve. Nifedipine also lowered the sensitivi of the coronary artery to serotonin and reduced t maximal constrictor response, a response compatib with the concentration-response curves in the isolat coronary ring (Fig. 7).

Discussion

In these experiments we have qualified the potenc and magnitude of a variety of constrictor substances o the coronary artery in the controlled environment of t organ bath where neural, hormonal and metabol changes can be eliminated. In the blood-perfused LA preparation, we could determine direct effects of co strictors and antagonists on coronary diameter witho the influences of blood flow and pressure change Therefore, these 2 preparations have allowed a mo rigorous analysis of the responses of the large coronar artery than is possible in man or in the intact myoca dium in experimental animals.[2]

Vasospasm: Vasospasm, defined as 0 luminal di ameter, was not observed in the experimental prepa rations of the LAD during infusion of high concentra tions of constrictor agents. The maximal decrease i luminal diameter was about 20 to 30%, a reduction tha would be unlikely to influence flow, especially if th constriction was confined to a few isolated sites. How ever, these dog coronary arteries were essentially nor mal, without atheromatous lesions, and were denervate by removal from the donor dog. Under appropriat conditions, one may be able to observe vasospasm ini tiated by a relatively small decrease in luminal diameter Such an amplified response could occur at sites of rel atively small atheromatous lesions,[6,12] where lumina encroachment or medial hypertrophy would lead to a greater decrease in luminal diameter for a given con strictor stimulus.

Another factor that may amplify the response t constrictor stimuli is low coronary pressure. Our ex periments show that the diameter of a large coronary artery decreases to a significantly lower level in the

presence of a constrictor substance when the perfusion pressure was reduced from 90 to 60 mm Hg. Therefore, 1 explanation of recurrent nocturnal pain that[13] wakes patients from sleep (13 of 17 patients, all with rest pain) could be that lower arterial pressure during sleep amplifies the constrictor response to some stimuli.

Possible mediators of coronary spasm: Experiments on isolated coronary rings suggest that ergometrine is a potent coronary artery constrictor substance acting as a serotonin agonist.[11] Similar conclusions have been reported previously.[14,15] The specificity of ergometrine as a diagnostic agent in variant angina may indicate a role for serotonin, perhaps released from platelets at the site of a minimal lesion. Platelets also produce thromboxane A_2(TxA_2), a product of arachidonic acid metabolism that is a powerful vasoconstrictor agent and an inducer of both platelet aggregation and the platelet release reaction.[16] TxA_2 is very unstable, at 37° at pH 7.5 with a half-life of 30 seconds, making it very difficult to define responses quantitatively. Therefore, we used the stable analog of TxA_2, U46619, which has a potent constrictor action similar to TxA_2 in human and dog coronary artery.[17,18] Although TxA_2 is a candidate for initiating vasospasm, clinical trials with synthesis inhibitors have been disappointing.[19]

Norepinephrine may also be a trigger stimulus for vasospasm. Coronary artery ring segments, however, did not contract consistently to this catecholamine added to the organ bath unless beta-adrenoceptor blockade was present. In the perfused coronary artery, norepinephrine infused into the lumen caused a small increase in diameter, which was also blocked by propranolol. These experiments do not support a role for circulating catecholamines in initiating coronary constriction. However, sympathetic nerve stimulation experiments may provide a clue to neurogenic vasospasm. Adjacent 3-mm segments from the circumflex coronary artery react very differently both in direction and magnitude of response to 10-second periods of stimulation. Therefore, it may be possible for a small segment to respond with marked constriction, although adjacent segments are less responsive. The receptors stimulated by the released norepinephrine are clearly alpha- and beta-adrenoceptors, as seen from the effects of the antagonists phentolamine and propranolol. Moreover, the density and type of adrenoceptor may vary along a large artery.

Because beta-adrenoceptors are apparently innervated in large coronary arteries, the use of beta-adrenoceptor antagonists could raise the incidence of episodes of variant angina by reducing neurogenic dilator tone. Indeed, this has been reported for propranolol in a small number of patients in a recent trial.[20] Theoretically, if beta-adrenoceptors in coronary arteries were of the $beta_2$ subclass, then a selective $beta_1$-adrenoceptor antagonist may still be useful in the treatment of variant angina.[21] This does not appear to be the case for large coronary arteries, at least from the dog, where agonist and antagonist studies showed some evidence for a $beta_1$-adrenoceptor classification.[22] Our studies showed that the so-called selective $beta_1$-adrenoceptor antagonist metropolol[23] amplified the constrictor response to sympathetic stimulation. We deliberately chose a concentration of metoprolol (50 ng/ml) that was within the range of peak plasma levels (20 to 198 ng/ml) observed in patients receiving metoprolol therapy for typical angina pectoris.[24,25] Therefore, beta-adrenoceptor blockade with nonselective or selective ($beta_1$) adrenoceptor antagonists may also act as an amplifier of focal neurogenic vasoconstriction.

Nifedipine, verapamil, and glyceryl trinitrate: Constrictor substances may vary in their requirement

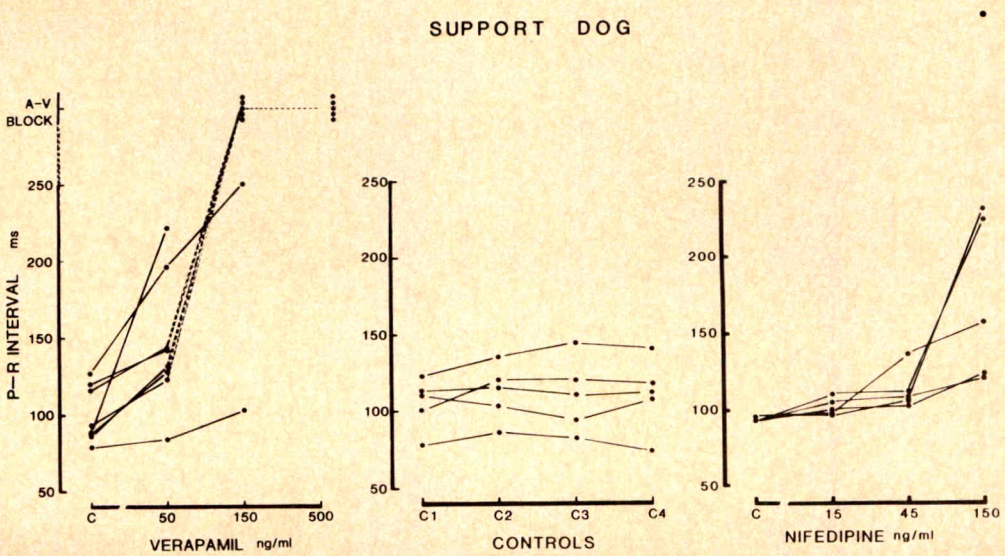

FIGURE 13. Effect of verapamil and nifedipine on the atrioventricular conduction (P-R interval in milliseconds) in the support dog. Each line represents the value for 1 experiment. Readings are the average of 3 to 6 intervals measured from lead II electrocardiogram, recorded just before the start of each of 4 serotonin curves.

for extracellular and intracellular calcium for activating contraction. Therefore, if dilator agents act by blocking the slow calcium channel without affecting the calcium release from intracellular stores, then only constrictors dependent on extracellular calcium should be sensitive to these antagonists. Both verapamil and nifedipine are classed as slow calcium channel blockers,[10,26,27] so they should have similar relative potencies against a range of constrictor agents. This is clearly not the case in the present studies, since nifedipine was 100-fold more potent against potassium-depolarized arteries than against serotonin or phenylephrine, whereas verapamil was similar in potency against serotonin and potassium but 3-fold less potent against phenylephrine. Similar selectivity by verapamil or methoxy verapamil (D600) has been noted in dog coronary[28] and in rat aorta.[29] Nifedipine has also been shown to be more potent against potassium than phenylephrine or serotonin in dog femoral arteries.[30] Therefore, verapamil and nifedipine have very different constrictor selectivities and the present classification of these drugs into a single class appears to be inadequate. In contrast with the calcium antagonists, the dilator action of glyceryl trinitrate was relatively nonselective of the constrictor agents consistent with an intracellular mechanism attributed to the formation of active, unstable, intermediate s-nitrosothiols.[31]

These studies emphasize that the success of using slow calcium-channel blockers to treat coronary vasospasm will depend to some extent on the nature of the constrictor stimulus. For example, verapamil would appear most useful against serotonin-induced constriction but would be much less effective against noradrenaline and almost inactive, perhaps, against thromboxane A_2. However, the studies in vivo suggest that there are other important differences between nifedipine and verapamil. We chose to administer both calcium antagonists at a dose to bring the plasma levels into a range that would be found therapeutically. For verapamil, this is 15 to 100 ng/ml.[10,32] Verapamil (50 and 150 ng/ml) was comparable to nifedipine (15 and 45 ng/ml) with regard to the antagonism of the serotonin constrictor response in the perfused coronary artery. However, verapamil appeared to be much more effective than nifedipine in depressing the sinoatrial node, abolishing reflex tachycardia, and lengthening the atrioventricular conduction time. These experiments, performed under barbiturate anesthesia, may have potentiated the effects of verapamil on nodal tissue. Nevertheless, a marked difference between the 2 calcium antagonists was observed. It is difficult to predict what degree of large coronary artery constriction would be required to trigger an episode of vasospasm in patients. It is equally hazardous to suggest from these experiments what degree of blockade is necessary for the calcium antagonists to be effective in vasospasm. What is clear, however, is that the actions of calcium antagonists are not confined to the large coronary artery at concentrations that are effective in reducing serotonin-induced constriction. Perhaps other actions of the drugs related to a decrease in myocardial oxygen consumption are just as important in the treatment of variant angina as in angina of effort.

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The Isolated Human Epicardial Coronary Artery

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Ring segments from coronary arteries from recipient hearts of patients receiving cardiac transplants were prepared and mounted in an organ bath. Spontaneous contractile activity, factors that affect basal tone, agonist-induced contractile responses, regional receptor distribution, activity of cardioactive drugs, and species differences were studied. Agents that mediate contraction include histamine, acetylcholine, norepinephrine, potassium and some prostaglandins. Calcium-entry blockers, nitrates and beta-adrenergic agonists caused relaxation. Major species differences exist in coronary vascular pharmacology. Ring segments from human epicardial coronary arteries are suitable for pharmacologic studies, and because of species differences, they offer an ideal model for investigating the pharmacology of the human coronary circulation.

For several years we have conducted clinical investigations of the pathogenesis, diagnosis and treatment of coronary artery spasm.[1–6] These and other studies suggest that the human epicardial coronary artery is not just a passive conduit through which blood flows, but a highly dynamic, reactive vascular structure that is subject to functional alterations by a variety of influences. To investigate the pathophysiologic mechanisms of spasm, we studied the pharmacology of human coronary vascular smooth muscle using isolated ring segments of human coronary arteries derived from both normal and diseased hearts. Although these types of in vitro studies provide interesting and useful data, extrapolation to intact systems must be made with caution, because these studies focus on only a single aspect of the many variables that exist in vivo. Nevertheless, we believe these techniques help to elucidate both pharmacologic mechanisms involved in human coronary arterial smooth muscle contraction and the pathophysiologic processes involved in coronary artery spasm.

General Methods

The cardiac transplant program at Stanford Medical Center provides us with the coronary arteries from normal and diseased hearts. We have performed pharmacologic studies on >1,000 coronary artery segments from 43 human hearts.

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The human coronary arteries were studied using a specially designed 12-chamber muscle bath and classic pharmacologic techniques. The right, left and circumflex epicardial coronary arteries were removed from the heart, cleaned of all adherent fat and connective tissue, and sectioned into 5-mm ring segments. The segments were mounted and placed under 1.2 g of tension. Equilibration time was 60 to 90 minutes. The physiologic solution was standard Tyrode's solution, except that the calcium concentration was slightly lower—2 m*M* calcium chloride. This yielded an ionized calcium measured by ion-specific electrode of 1.26 m*M*, which is similar to that of human serum. The bath was kept at 36°C, pH 7.40 to 7.45, and each bath was aerated with 95% oxygen and 5% carbon dioxide.

The coronary arteries were obtained immediately upon removal of the recipient heart from the transplant patient. Bovine, porcine and canine coronary arteries were also studied in an attempt to characterize species differences; this material was obtained from other laboratories or from slaughterhouses.

Basic Pharmacologic Characteristics of Human Coronary Artery

Basal tone: We define basal tone as the tension generated by the resting coronary segment. Human coronary ring segments exhibit basal tone, and this tone is calcium-dependent. This is found in innervated as well as denervated coronary arteries. Tone is also found in atherosclerotic ring segments; only in severely diseased segments with marked calcification is tone not consistently found.

TABLE I Effect of Drugs on In Vitro Human Coronary Artery Ring Segments

Contraction	Relaxation
Histamine (H_1)	Nitroglycerin
Norepinephrine	Diltiazem
Phenylephrine	D-600
Carbachol	Verapamil
Calcium	Nifedipine
Potassium	PGI_2 ($<10^{-6}M$)
TEA	Histamine (H_2)
Ergonovine	Isoproterenol
Serotonin	Sodium azide
$PGF_{2\alpha}$	
PGE_1	
PGE_2	
PCH_2	
PGI_2 ($>10^{-6}M$)	
Indomethacin	

Inhibition of specific receptors with adrenergic, histaminic or muscarinic blocking agents does not affect basal tone. Of the endogenous vasoactive substances that act through a receptor mechanism, prostaglandins appear to be the only class of compounds that influence basal tones. Prostacyclin, which is a potent relaxer of coronary arteries, is produced by the endothelial cells of the artery.[7] The addition to the bath of prostaglandin synthetase inhibitors, such as indomethacin or ibuprofen, causes contraction of the coronary segment from its basal state, probably by inhibiting the synthesis of prostacyclin production. The importance of prostaglandins in regulating tone has been shown in bovine coronaries,[8] and we have demonstrated similar findings in human tissue (Table I).

"Transient" contractile responses of isolated vascular smooth muscle to norepinephrine correlated well with basal tone have recently been proposed by Bevan.[9] If there is such a correlation, then the human coronary artery is another example, because transient contractile responses are seen in response to norepinephrine. These transient responses are due to the release of "intracellular" calcium stores, but whether this mechanism is crucial for the regulation of tone is unknown.

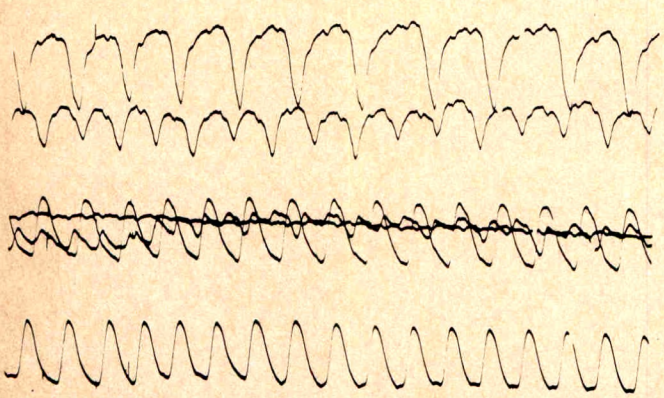

FIGURE 1. Simultaneous recording of 6 human coronary ring segments. Five of 6 segments show rhythmic periods of contraction and relaxation.

Spontaneous and induced phasic, rhythmic myogenic activity: Human coronary ring segments demonstrate spontaneous, rhythmic periods of contraction and relaxation.[10] This rhythmic activity has been described in veins and arteries from a variety of vascular beds and animal species.[11] Although a fascinating phenomenon, the physiologic role of such spontaneous activity is unknown (Fig. 1).

In human coronary arteries, this cyclic activity is usually very uniform, with cycle lengths of 60 to 80 seconds. Various agonists can induce the rhythm and change amplitude and cycle length. Not all segments have spontaneous rhythmicity, and there is no 1 characteristic that identifies which arteries will or will not demonstrate this type of activity.

Phasic, rhythmic contraction has been observed in human coronary segments from any of the 3 major arteries. This phenomenon must induce synchronous contraction of many cells of the ring segment and thus demonstrates single-unit organization in vascular smooth muscle. For this synchronization to occur, some type of communication system is needed. Electron micrographs have revealed nexuses or gap-junctions between smooth muscle cells. These have been described in other types of vascular smooth muscle cells and are thought to be the pathway for electrical activity.[12]

Electrophysiologic studies imply that action potentials generated from a pacemaker focus are propagated along the coronary segment through these nexuses, which permit synchronization of electrical and mechanical activities.

Rhythmic activity is affected by environmental factors and various vasoactive substances. Changing the bathing fluid to a more alkaline state increases cyclic amplitude, but not frequency. An acid pH causes cessation of all activity. Cold and hypoxia also cause decreased rhythmic activity. Vasoactive substances that induce activity in quiescent ring segments include norepinephrine, acetylcholine, histamine, prostaglandin-E_2 (PGE_2) (in high doses), ergonovine and potassium. Nitroglycerin, lidocaine, D-600 and diltiazem cause cessation of rhythmic activity. Thus, rhythmic activity can be regulated and controlled through the interaction of many variables.

Previous neural innervation is not necessary for rhythmic activity, because there is no difference between denervated or innervated ring segments. Rhythmic activity is not affected by alpha- or beta-adrenergic, muscarinic or histaminic-blocking agents. This spontaneous rhythmicity occurs in normal or diseased coronary arteries, but the cyclic pattern and frequency in atherosclerotic segments is usually quite irregular. This may be the result of a degenerative process involving the nexuses.

The functional importance of action potentials, pacemaker foci, conduction pathways and the resulting rhythmic activity is unknown. However, we do know that any segment of a coronary artery can exhibit this activity and secondarily generate large forces of contraction. It is interesting to speculate that the clinical phenomenon of focal spasm might involve a triggering

of electromechanical activity through the voltage-sensitive pathway.

Agonist-induced vascular smooth muscle contraction: Brodie et al[13] originally separated agonist-mediated contractile responses into 2 types, one operating at a faster rate than the other. Subsequently, Bohr[14] demonstrated that the dual effects of calcium on membrane excitation and its coupling to contraction could be seen in a single contractile response to an agonist. He separated the epinephrine-induced contraction into 2 components, a phasic or fast component and a tonic or slow component. Sitrin and Bohr[15] later demonstrated that the fast component used cellular bound calcium and that the rate-limiting factor for the release of this bound calcium was the excitability of the cell membrane.[15] These investigators and others[16] showed that the slow component was dependent upon extracellular calcium, in that this part of the response was readily inhibited in a calcium-free solution and was increased as the concentration of calcium was raised toward physiologic levels. The slow component of the norepinephrine response was also accompanied by an increase in calcium-45 uptake.

The human coronary artery responds to stimulation by an agonist with a similar biphasic response. This biphasic response has been studied in detail in the rabbit aorta and rabbit ear artery. The initial rapid phase of contraction is believed to be partially due to the release of tightly bound or "intracellular" calcium. Whether this "intracellular" calcium comes from sites located in sinks on the inner surface of the plasma membrane, from the sarcoplasmic reticulum, or from the mitochondria is not known. The slow, tonic phase of contraction, the other portion of the biphasic response, is believed to be a result mainly of the influx of freely exchangeable or extracellular calcium through the calcium "slow channels" located in the cell membrane.

The biphasic response is found only in certain vascular beds.[17–19] It has been quite a consistent observation in our coronary artery studies and probably reflects differences in calcium stores and mechanisms for release compared with other vascular tissue. The initial phasic response by the human coronary ring segment is a rapid contraction (Fig. 2) and can, depending on the agonist, account for 70% of the overall maximal tension generated. If the same response is elicited in a calcium-free solution, it can generate up to 20 to 50% of the maximal tension produced by the segment in a "normal" (1.26 m*M*) calcium solution. This suggests that the release of intracellular calcium contributes significantly to overall contraction of human coronary vascular smooth muscle.

The characteristics of the slow, tonic phase in human coronary arteries are similar to those in other animal models. This phase is presumably due to the influx of "extracellular" freely exchangeable calcium. In our studies in calcium-free solutions, no tonic response can be observed during an agonist challenge (Fig. 3).

Species differences: We compared the characteristics of coronary arteries from the dog, pig and cow using the same techniques as those used for man. Dose-response curves to a variety of agonists were compared, receptor distribution was analyzed, and basal tone and rhythmic vasoactivity were evaluated.

Our results have shown a marked variation in sensitivity of the contractile response to various agonists among animal models. No animal has all the features found in man. These differences have been quite impressive and suggest that care should be taken when selecting a species for study in an in vitro setting. Whether these differences are present in the intact animal model is not known.

In the canine coronary artery, Van Breemen et al[20] showed that in response to norepinephrine there is only

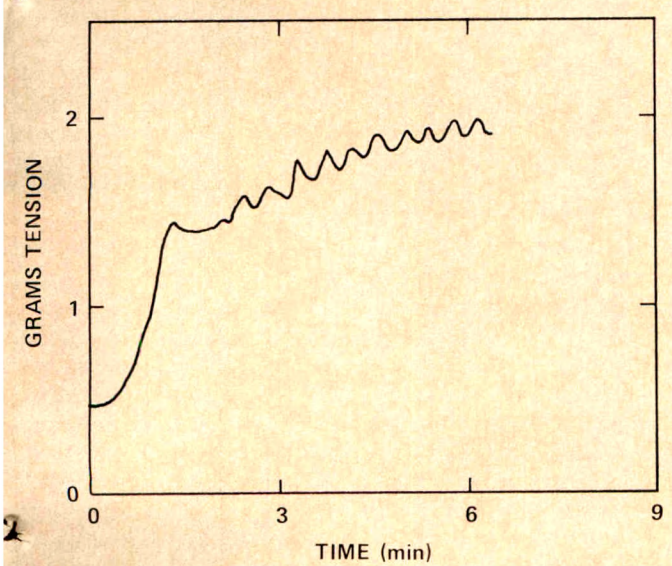

FIGURE 2. Contraction pattern of single human coronary artery ring segment to a receptor-mediated vasoactive agent, histamine. There is a rapid rate of contraction initially, and then a slower, tonic phase of contraction over several minutes.

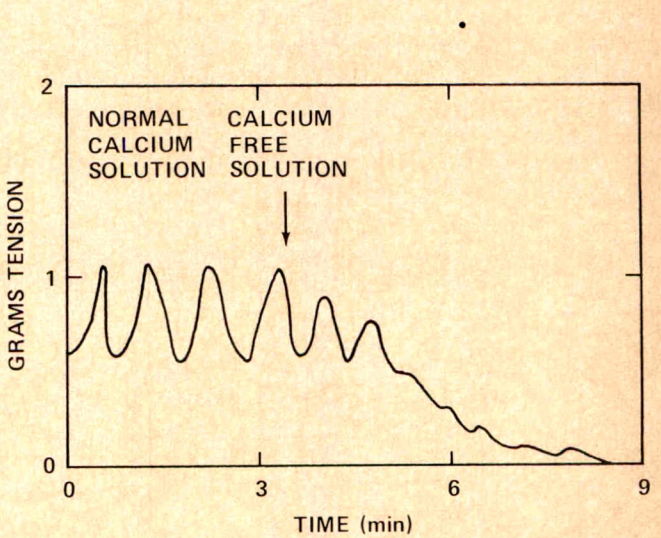

FIGURE 3. Contraction pattern of single human coronary artery ring segment in a normal and 0-calcium environment. Basal tone decreases with the removal of calcium.

an influx of extracellular calcium and no release of intracellular calcium. This is in contradistinction to the rabbit, pig or human coronary artery, which use both pools in response to norepinephrine stimulation.

Norepinephrine: The exposure of the human coronary artery ring segment to phenylephrine or norepinephrine in the presence of propranolol results in contraction of the segment. The maximal grams of tension that a segment generates in response to these drugs is usually less than to other agonists we have studied. However, the sensitivity to these drugs (median effective dose $10^{-7}M$) is similar to that found in other animal species. Unlike the canine coronary artery, the human coronary artery mobilizes 2 pools of calcium for contraction upon exposure to norepinephrine. There is both the influx of extracellular calcium and the release of intracellular calcium. The canine coronary artery uses only extracellular calcium.[20]

The contribution of the adrenergic nervous system to coronary vasoregulation has been intensively investigated. Studies in the intact dog have shown that coronary blood flow can be influenced markedly by stimulation or blockade of the alpha-adrenergic receptors that supply the large coronary arteries. Therefore, much emphasis has been placed on the neurogenic influence on the coronary circulation.[21]

Recently, Ricci et al[22] described altered adrenergic activity in patients with coronary spasm. They demonstrated that phentolamine could reverse coronary spasm and decrease coronary vascular resistance. The mechanism of action of phentolamine, however, is not completely known. Although it is an alpha-antagonist in vitro, it may have direct smooth muscle effects. Studies with long-acting alpha blockers such as phenoxybenzamine have not demonstrated uniform effectiveness in the treatment of spasm, and therefore, the role of the adrenergic system in mediating coronary spasm is questionable.

Thus, although sympathetic nerves, norepinephrine and alpha-adrenergic stimulation may play a role in the contraction of the human coronary artery, data from muscle bath studies suggest that this is not the only mechanism, nor is it the most important, either in normal physiologic processes or in pathophysiologic states such as vasospasm.

Acetylcholine: In the human coronary ring segment, acetylcholine stimulation results in contraction. Its potency lies between norepinephrine and histamine. Receptor population also changes along the length of the vessel. Of interest is the marked variability in animal models; the dog has essentially no response to acetylcholine.

Methacholine has been used in human studies to provoke coronary spasm.[23] It may operate by the indirect stimulation of the sympathetic nervous system, provoking spasm through alpha-adrenergic receptors. In vitro, this mechanism is not necessary because acetylcholine itself causes contraction of the coronary segment. Acetylcholine or carbachol is operating through a specific membrane receptor.

Histamine: The sympathetic nerves, cardiac muscle and coronary arteries are rich in mast cells and histamine. Histamine is released into the circulation during sudden withdrawal of sympathetic tone and after direct stimulation of sympathetic nerves and spinal nerve roots.[24] Therefore, it has a regulatory role in adrenergic neurotransmission. Histamine, along with acetylcholine, angiotensin, prostaglandins and norepinephrine, can alter the neurotransmitter by acting on sympathetic nerve endings. In the tissue bath, histamine can cause a potentiation of norepinephrine effects in vascular smooth muscle.[25] Thus, histamine may play a role in coronary vasoregulation.

In human coronary segments histamine is not very potent (median effective dose $1 \times 10^{-5}M$), but it does generate 1 of the greatest contractile responses in terms of grams of tension of the agonists studied. As reported previously,[26] this contraction is mediated by an H_1 receptor subtype. Also of interest is that histamine always induces rhythmic, myogenic activity. Receptor distribution analysis has demonstrated more H_1 receptors proximally than distally along the length of the artery.

Prostaglandins: Prostaglandins have been studied in in vitro preparations, including human coronary arteries.[7] Our data indicate that prostaglandins are significant mediators of basal tone.

As has been shown previously, PGE_1, PGE_2 and $PGF_{2\alpha}$ can cause contraction of the human coronary artery. PGI_2, however, is usually classified as a potent coronary smooth muscle relaxant. In the human coronary segment, PGI_2 gives a biphasic response. At low doses, it is a potent relaxer, but at higher concentrations ($>10^{-6}M$), PGI_2 produces a contractile response that is similar to that of all other vasoconstrictors studied. Therefore, a prostaglandin known to be produced in the vessel wall of the human coronary artery can cause contraction or relaxation.

Prostaglandins are formed by the enzymatic oxygenation of certain polyunsaturated fatty acids. Released prostaglandin precursor (such as arachidonic acid) is acted upon by cyclooxygenase, resulting in the formation of the cyclic endoperoxide PGH_2). In the rabbit aorta and in porcine and human coronary arteries, PGH_2 is a potent vasoconstrictor, and acts primarily on the intracellular calcium pool. In the bovine coronary artery, PGH_2 causes relaxation,[27] emphasizing that species differences do exist and that generalizations cannot be made about human pharmacology strictly from animal experiments.

Ergonovine: Although not an endogenously produced substance, ergonovine most consistently provokes coronary spasm clinically. Although ergonovine and other ergot alkaloids are known stimulators of smooth muscle contractions,[28] they have not been intensively investigated in coronary artery smooth muscle. Studies in the human coronary artery show that ergonovine operates partially through an alpha membrane receptor. Rabbit studies indicate that ergonovine operates more specifically through a serotonin-type receptor. Although ergonovine constricts the human coronary artery, the maximal grams of tension generated is the least of all agonists studied to date. Its action in vivo especially in provoking coronary spasm may not be a result of direct

stimulation of a specific receptor, but may be indirect through the release of other mediators. Understanding the pharmacologic mechanism of action of ergonovine may elucidate the pathophysiology of spasm.

Calcium-entry blockers: Fleckenstein[29] and others have examined the pharmacology of calcium blockers in vascular smooth muscle. The calcium blockers are clinically important in the treatment of arrhythmias, coronary spasm, exertional angina pectoris and cardiomyopathies.

The human coronary artery has at least 2 operational membrane calcium channels. One is a voltage-sensitive pathway and the other is a receptor-operated channel. The voltage-sensitive pathway can be activated by depolarization with high potassium. This voltage-sensitive pathway is exquisitely sensitive to calcium-entry blockers such as D-600, diltiazem, nifedipine and verapamil. Administration of these blockers eliminates basal tone and myogenic rhythmicity—physiologic phenomena operating through the voltage-sensitive pathway. The receptor-operated pathway is blocked by calcium antagonists only at high concentrations, when their activity is probably "nonspecific" in nature. Also, the release of intracellular calcium is not inhibited by these channel blockers. The observation that calcium blockers affect only the voltage-sensitive pathway is an important clue in understanding the mechanisms of spasm.

Some calcium-entry blockers exhibit selectivity in the human heart by blocking calcium entry in the coronary artery more than in the myocardium. Diltiazem is 10-fold more sensitive on the coronary bed than on cardiac muscle. D-600, nifedipine and verapamil are not selective, and block calcium entry at equimolar concentrations in the coronary arteries as well as the myocardium. This difference has clinical significance when using these agents in patients with left ventricular dysfunction.

In the human coronary artery, calcium-entry blockers eliminate basal tone. They also cause relaxation of segments that are contracted by potassium or their vasoactive agents. Relaxation is a slow process, but at high doses these blockers cause complete relaxation of the segments. It appears that these blocking agents are operating solely through the voltage-sensitive pathway.

Nitroglycerin: Although nitrates have been used clinically for >100 years, their mechanism of action is not fully understood. In the human coronary segment, nitroglycerin causes immediate relaxation of the segments. This relaxation is only 20 to 40% of that achieved by calcium-entry blockers, although it occurs more rapidly. The responses of nitrates and calcium-entry blockers are additive in the muscle bath; this is seen clinically in patients taking these drugs.

Nitrates are not calcium-entry blockers, and are in a different pharmacologic class. Nitrates act intracellularly and appear to remove or inactivate a portion of calcium used in contraction. Whether this involves cyclic guanosine monophosphate is not clear. Further research is still needed.

Atherosclerosis: Coronary artery spasm usually occurs in areas of atherosclerosis. Recent studies of dog coronary arteries have shown that cholesterol sensitizes coronary vascular smooth muscle to the effects of external calcium by a nonadrenergic mechanism.[30] Thus, it is postulated that cholesterol may alter the contractile properties of the muscle or the cell membrane. Rabbits fed high-cholesterol diets have increased sensitivity to ergonovine and serotonin, but not to norepinephrines. These animal studies and clinical studies have suggested altered pharmacology in areas of atherosclerosis.

In our studies on human coronary segments, there was increased sensitivity to histamine in atherosclerotic compared with normal segments. There was no change in sensitivity to carbachol, calcium or norepinephrine. Thus, atherosclerosis apparently can affect membrane receptors, and increased sensitivity on up-regulation can occur to specific vasoactive agonists. The role for this supersensitivity in the pathophysiology of coronary spasm is being investigated.

In summary, the human coronary artery studied in vitro has enabled us to characterize responses to a variety of agonists, examine contractile responses, identify receptor subtypes and distribution, and delineate species differences. Whether these observations have direct correlates in the in vivo setting is unknown, but these types of pharmacologic studies allow us to study a single organ in detail without the influence of local mediators or blood-borne agents. Our studies have characterized the responses to endogenous vasoactive agents and other cardioactive drugs, such as calcium-entry blockers. Two operational calcium membrane channels have been identified, as well as the functional calcium pools used in contraction. These studies may help elucidate the pathophysiology of coronary artery spasm and vascular supersensitivity in areas of atherosclerosis.

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Clinical Studies of Patients With Coronary Spasm

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Coronary artery spasm may cause myocardial ischemia in patients without severe coronary atherosclerotic obstruction. Spontaneous rest angina, particularly at night, is the predominant symptom; most patients are smokers. Ergonovine tests have high sensitivity and specificity for the diagnosis of coronary spasm, but should be used when vasospasm is suspected but no electrocardiogram was recorded during spontaneous angina. Arterial constriction measured during ergonovine testing suggests that the arterial hypersensitivity to vasoconstrictors at sites of atherosclerotic lesions is independent of the severity of the lesion. Coronary vasospasm may also be provoked by exercise, possibly through an alpha-adrenergic mechanism. Both spontaneous and exercise-induced attacks of vasospasm are prevented by calcium-antagonist drugs that remain effective during longer-term treatment. The cyclic nature of the condition is demonstrated when successful therapy is discontinued without recurrence of symptoms and may be due to alteration of arterial hypersensitivity.

Coronary artery spasm may cause angina in patients with and without severe atherosclerotic obstruction,[1,2] although another mechanism may be involved.[3,4] Patients with spasm but without severe organic stenoses are a more homogeneous group for pathophysiologic study, as in these patients ischemia is not caused by an increase in myocardial oxygen demand, but rather by reduced coronary blood flow and decreased vasomotor tone. This group forms the basis of this review.

Clinical Profile

Thirty-seven patients with angina due to spasm of arteries without severe stenoses were recently reviewed.[5] The male:female ratio was 3:1 and the mean age was 52 years. All patients had typical anginal pain at rest; in 86%, the pain was nocturnal. Forty-six percent had pain on exertion. Eighty-six percent were smokers, with an average tobacco consumption of 30 cigarettes/day. In 43%, there was a history of hypertension; 22% had a history of Raynaud's phenomenon and 27% had migraine headaches.

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Electrocardiographic and Angiographic Findings

The electrocardiogram in the absence of pain was abnormal in 59%, showing ST- and T-wave changes.[5] ST-segment elevation was the usual finding during spontaneous angina, although ST-segment depression was occasionally seen. Major arrhythmias during angina were documented in 27% of patients. Ventricular tachycardia or fibrillation was recorded in 24% and complete atrioventricular block in 5% (1 patient had both). The arrhythmia resulted in syncope in 19% and emphasizes that vasospasm without severe coronary disease may be lethal. Coronary angiography usually revealed minor degrees of coronary artery disease. Stenoses of 30 to 50% luminal diameter narrowing were present in 86% of the patients. The coronary artery most frequently involved by spasm was the left anterior descending, which differs from the preponderance of right coronary spasm reported in 2 other series.[6,7] Occasionally, spasm involved both arteries either simultaneously[8] or separately on different occasions.[9]

Diagnosis: Ergonovine Testing

Spontaneous coronary spasm occurs infrequently during routine angiography,[10] so methods for reliably provoking spasm have been sought. Ergonovine maleate (ergometrine) has become the most widely used drug for this purpose and is given either at the time of angiography,[11] or in the coronary care unit with 12-lead elec-

trocardiography or thallium-201 myocardial scintigraphy to detect the ischemia resulting from spasm.[8,12]

Protocols for ergonovine administration differ principally in the total dose administered and the interval between successive doses. We used a starting dose of 0.05 mg, and gave incremental doses every 3 to 5 minutes to a maximum of 0.65 mg.[8] Provoked spasm is usually reversible with sublingual nitroglycerin,[8] but parenteral preparations of nitrate or nitroprusside must be available and used promptly if there is any delay in the relief of spasm.[8] Cardiopulmonary resuscitation facilities should be available.

In a study of 69 patients with chest pain and no severe coronary atherosclerosis, all 5 patients with documented variant angina had a positive ergonovine test, suggesting a high sensitivity of the test.[8] The overall sensitivity in 47 similar patients pooled from 5 series was 91%.[11,13–16] The specificity of the test is also high: In 34 patients with chest pain atypical for myocardial ischemia, no spasm was provoked by ergonovine.[8] When these figures were pooled with the results from 3 other studies,[11,15,16] the incidence of false-positive test results in 173 similar patients was only 3%, confirming the high specificity.

Serious complications of ergonovine testing have been reported recently[16–18] and suggest that ergonovine should not be given to patients with documented variant angina, but restricted to patients with suspected vasospastic angina, without electrocardiographic confirmation during chest pain.[8,16] Prolonged ambulatory recording of 2 or 3 ECG leads may detect ischemic ST-segment changes during spontaneous chest pain. If ST-segment changes are not identified by Holter monitoring, ergonovine testing is indicated and will have positive results in 40 to 53% of these patients.

Pathophysiology of Coronary Spasm

Coronary spasm may be caused by an abnormal vasoconstrictor stimulus (either exaggerated physiologic or pathologic), or arterial hypersensitivity to physiologic vasoconstriction. Both mechanisms may also occur simultaneously. Ergonovine testing suggests that increased arterial sensitivity may cause spasm. When doses as high as 0.65 mg are given to normal subjects, mild vasoconstriction of 15 to 20% results, with no localized spasm.[13,19–21] In contrast, patients with documented variant angina have severe spasm at lower ergonovine doses,[8] suggesting they have increased arterial sensitivity to ergonovine. This arterial hypersensitivity is apparently nonspecific and occurs with many vasoconstrictors: methacholine,[22–24] alkalosis from hyperventilation or TRIS buffer infusion or both,[25–27] the cold-pressor test,[28] adrenaline with and without propranolol[22,29,30] and histamine.[31] A number of observations suggest that this hypersensitivity is localized to 1 coronary artery, usually at the site of coronary atherosclerosis.

Electrocardiographic changes usually recur in the same leads during repeated attacks of vasospasm in the same patient, implying that the same artery is usually involved.[32] Both ergonovine-induced and spontaneous spasm usually occur at the same site in the same patient.[11,33,34] The majority of cases of spontaneous or ergonovine-induced spasm occur at atherosclerotic lesion sites.[35] In patients with variant angina and a positive ergonovine test finding, the lesion itself and not the whole coronary arterial tree appears to be hypersensitive to ergonovine[13,19] or alpha-adrenergic stimulation.[30] Vasoconstriction at stenosis sites is greater in patients with clinical variant angina and positive ergonovine tests than in patients with chest pain atypical for myocardial ischemia and negative ergonovine tests (Fig. 1).[19]

MacAlpin[2] postulated that local arterial hypersensitivity results from normal vasoconstriction, amplified when the luminal cross section is already reduced by a lesion.[2] If a lesion is represented as a circumferential stenosis, and assuming that vasoconstriction in the normal segment is fully translated to the lesion and that the area of the vessel wall remains constant after vasoconstriction, then the vasoconstriction to be expected at a lesion site (x) may be given by the following ex-

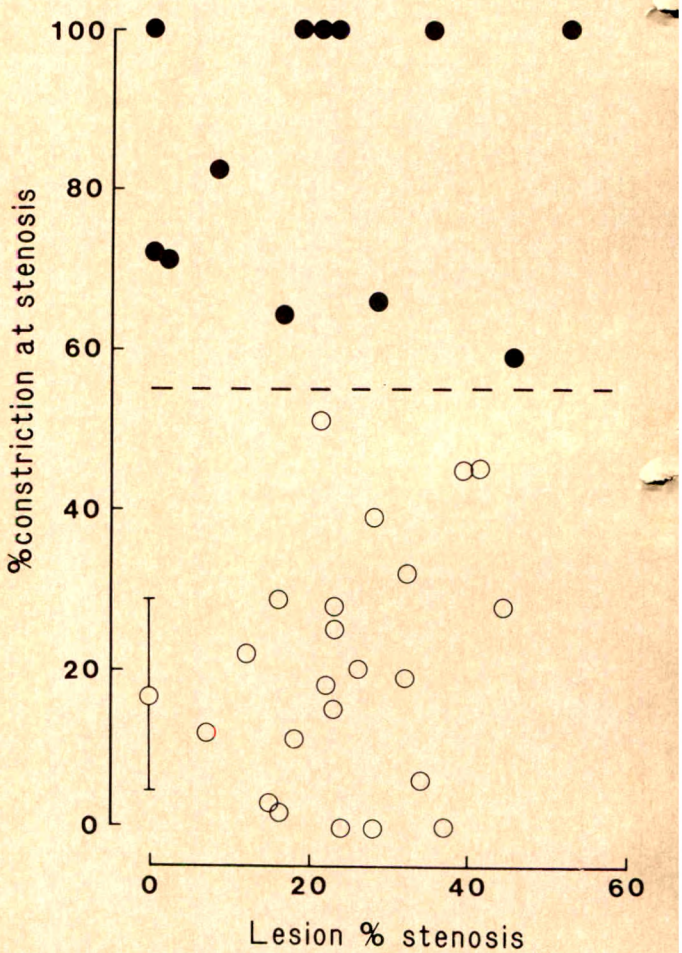

FIGURE 1. Percent constriction at a lesion site after ergonovine versus the severity of the stenosis for patients with clinical variant angina and positive ergonovine test results (**closed circles**) and patients with atypical chest pain and negative ergonovine test findings (**open circles**). The mean vasoconstriction (± standard deviation) for normal proximal arterial segments of patients with atypical chest pain is shown on the left for comparison. There was no overlap between the 2 groups of patients. **Dotted line** (55% constriction at a lesion) represents an arbitrary cut-off between negative and positive tests.

pression: $x = 100\,(1 - (1 - p/100) + (1 - y/100) - 1)/(1 - p/100)$, where p = percent stenosis of the lesion and y = percent vasoconstriction in the adjacent normal segment.[19] Using coronary angiograms before and after ergonovine administration, values could be measured for x, p and y.[19] The measured values of x were compared with values derived from equation 1 (Fig. 2). For patients with positive ergonovine tests, the observed vasoconstriction at lesion sites was always greater than that predicted by equation 1, indicating that geometric considerations alone do not explain arterial hypersensitivity at lesion sites. A similar conclusion can be drawn from the study of Brown et al,[30] which showed that lesions from patients with vasospastic angina were more sensitive to arterial vasoconstriction than lesions of similar severity from control patients.

The reason for arterial hypersensitivity at sites of atheroma is not known. Henry and Yokoyama[36] suggested that the presence of cholesterol in a lesion sensitizes the membrane to ergonovine and other constrictors, but atherosclerotic segments of human coronary arteries have been shown to be sensitive to histamine.[31] This mechanism cannot explain spasm in normal coronary arteries nor why only some atherosclerotic lesions are associated with spasm.

Exercise-Induced Coronary Spasm

Levene and Freeman in 1976[37] first suggested coronary spasm could occur during exertion. Yasue et al[38,39] demonstrated epicardial coronary artery spasm at angiography associated with ST-segment elevation during exercise; this has been confirmed by others.[40,41]

In our patients,[5] 13 of 30 (43%) with coronary artery spasm who exercised without therapy had angina and ST-segment elevation. A prevalence of 24 to 54% has been reported.[7,42,43]

Alpha-adrenergic vasoconstriction was postulated as the cause, because phenoxybenzamine suppressed the response in doses which shifted the phenylephrine dose-response curve.[37] In our own experience, 20 mg of phenoxybenzamine was effective in only 3 of 8 patients, although postural tachycardia or hypotension indicated that some alpha-adrenergic blockade had been produced. Fuller et al[44] found that 30 mg of phenoxybenzamine was ineffective in 2 patients; Yasue et al[39] reported 30 mg of phenoxybenzamine as effective in 3 of 4 patients, and phentolamine (0.2 mg/kg) effective in 6 of 9 patients.[38] The nonuniform response to alpha-blocking drugs may indicate that the degree of alpha blockade was not always sufficient to counteract the stimulus or that exercise-induced coronary spasm may be mediated by other mechanisms.

Yasue et al[39] described a diurnal variation in exercise coronary spasm. All 13 patients who exercised in the early morning had reproducible spasm, but only 2 also had spasm during exercise in the afternoon. Yasue[39,45] attributed this to a circadian rhythm of coronary artery smooth muscle tone; coronary diameters were smaller and responsiveness to nitroglycerin greater in the early morning. Although diurnal patterns were not specifically examined in our patients, all 10 who were exercised in the afternoon developed coronary spasm. One of our patients had a diurnal response to verapamil, requiring higher blood levels to prevent exercise coronary spasm in the morning than in the afternoon.[41] The difference in diurnal responses between series is not apparent.

The calcium-antagonist drugs verapamil,[41] diltiazem and nifedipine[38,39] are effective in preventing attacks of coronary artery spasm. In our own series of 13 patients, 11 were exercised again after pretreatment with oral verapamil. Verapamil alone was effective in 8 of the 11; in 3, additional nitrates were required to prevent spasm. Fuller et al[44] also described 2 patients in whom verapamil was ineffective, whereas isosorbide prevented exercise spasm. The dosage of drug is important to prevent exercise spasm. The results from 3 patients with

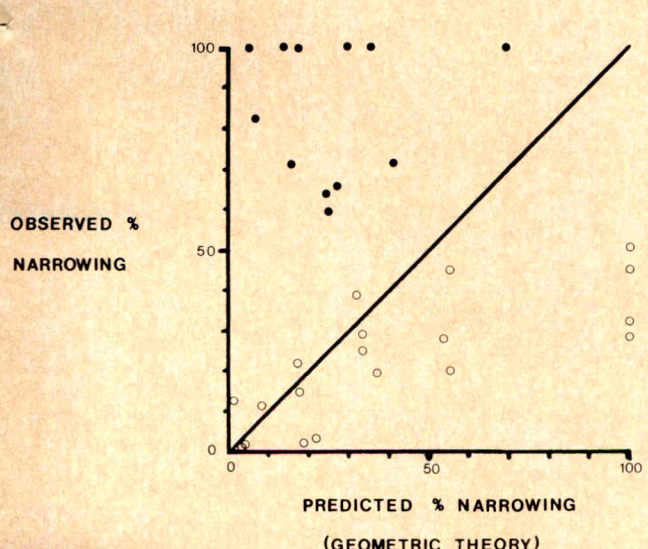

FIGURE 2. Predicted percent narrowing versus observed percent narrowing at lesion sites in patients with positive (**closed circles**) and negative (**open circles**) ergonovine tests. The line represents identity between observed and predicted values. Observed values from patients with a negative test fell on or below the line, while values from patients with a positive test were all above the line.

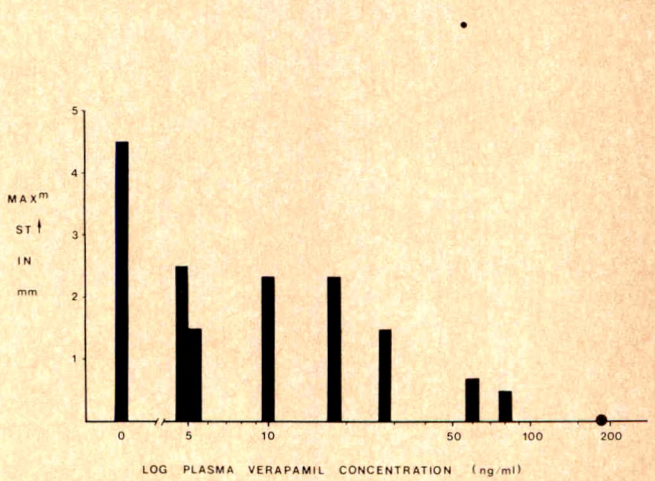

FIGURE 3. Maximal degree of ST-segment elevation (**vertical bars**) during repeated exercise tests versus plasma verapamil concentration in patients with reproducible exercise-induced coronary spasm. With increasing concentrations of verapamil, there was progressively less ST-segment elevation, and the test was negative (**circle**) at a concentration of 191 ng/ml.

reproducible exercise-induced spasm treated with different doses of verapamil are shown in Figure 3. The height of the vertical bars, representing the maximal amount of ST-segment elevation during exercise, shows a progressive decrease with increasing plasma concentrations of verapamil, until the test is completely negative at a plasma concentration of 191 mg/ml (circle). The range of verapamil plasma concentrations required to inhibit exercise spasm in these patients is within the range of plasma concentrations achieved by dosage with 320 mg/day (80 mg every 6 hours).[41,46,47] Spontaneous angina was also prevented by the same mean dose of verapamil in a larger group of patients,[5] indicating that therapeutic levels of verapamil are probably similar for both exercise-induced and spontaneous coronary spasm.

Medical Therapy for Coronary Spasm

Nitrates are usually effective in relieving acute attacks of spasm, but are ineffective for prophylaxis.

All calcium-antagonist drugs are effective in preventing coronary artery spasm.[5,48] Nifedipine, verapamil and diltiazem are equally effective if used in appropriate dosage.[49–53] Long-term verapamil alone or with isosorbide dinitrate has been very useful for the prevention of coronary spasm.[5] Of 37 patients, 32 became asymptomatic or satisfactorily controlled, and 3 of the remaining 5 achieved control by substitution of nifedipine for verapamil. The symptomatic response was maintained during a follow-up for a mean of 21 months. The mean dosage of verapamil was 320 mg/day and of nifedipine was 60 mg/day. No patient had myocardial infarction or died during the follow-up study.

In some patients, successful long-term medical therapy can be withdrawn without recurrence of angina.[5] In such patients, ergonovine tests, using the same or higher doses as had previously provoked spasm, were no longer positive.[54] This implies that the arterial hypersensitivity to ergonovine previously demonstrated was no longer present.

Clinical Implications

Coronary artery spasm may cause myocardial ischemia both at rest and during exertion, and should be suspected in patients with typical anginal symptoms at night or in the early morning. The underlying cause appears to be coronary arterial hypersensitivity to a number of vasoconstrictors at sites of minor atherosclerosis. Treatment should be directed toward preventing arterial smooth muscle constriction. The calcium-antagonist drugs are clinically effective in preventing episodes of coronary spasm.

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Pathobiology of Acute Myocardial Ischemia: Metabolic, Functional and Ultrastructural Studies

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Acute myocardial ischemia induced by coronary occlusion in dogs is most severe in the subendocardial region, whereas more collateral blood flow is often present in the subepicardial region. Initially, all ischemic myocytes are reversibly injured, but beginning at 15 to 20 minutes after the onset, and continuing for 3 to 6 hours, there is a wave front of cell death from the subendocardial region to the less ischemic subepicardial region, such that by 6 hours, the final transmural extent of the infarct is established. Thus, ischemic myocardium cannot be salvaged by reperfusion after ≥6 hours of coronary occlusion in open-chest anesthetized dogs.

In the severely ischemic subendocardial region, most of the creatine phosphate is lost within the first 3 minutes of ischemia in vivo, and adenosine triphosphate (ATP) is depleted to 35% of control by 15 minutes (when cellular injury is still reversible), and to <10% of control at 40 minutes (when injury is irreversible). Tissue ATP content and other indexes of subcellular damage have also been compared after different periods of ischemia using a model of total myocardial ischemia in vitro. As long as the ATP of the tissue was not depleted below μmol/g dry weight, incubated slices of injur myocardium resynthesized high-energy phosphat and excluded inulin. However, lower tissue ATP w associated with depressed high-energy phospha resynthesis and failure of cell volume regulatic Overt membrane damage, as measured by an i creased inulin-diffusible space, was detected or after the tissue ATP decreased to <2.0 μmol/g dry weight. Thus, marked ATP depletion is assoc ated with the onset of structural and functional i dexes of irreversible injury. However, whether reversibility is caused by the marked ATP depleti or by other concomitant metabolic consequenc of ischemia is not known. Myocardial ischem cellular injury is reversible despite depletion of 70 of the control ATP. Nevertheless, when myocy injury is reversible, there is slow repletion of adeni nucleotides. This slow metabolic recovery m explain the delayed recovery of contractile functi observed after reperfusion of ischemic myoca dium.

Severe ischemia has been defined as a reduction in coronary arterial blood flow to ≤15% of control.[1] In the dog heart, this develops in the subendocardial region of the myocardium when the circumflex artery supplying this region is occluded near its origin. Myocytes will tolerate 15 minutes of ischemia of this severity, that is, they survive if flow is restored after this interval. Thus, the injury induced by up to 15 minutes of severe ischemia is *reversible*.[2] In contrast, if ischemia is allowed to persist for 40 minutes before arterial flow is restored, many of the cells in the subendocardial region of seve ischemia die. The cells that do not survive when isch mia is eliminated undergo phagocytosis and are replac by scar tissue; thus, the injury is *irreversible*.

By 40 minutes of ischemia, cell death in the sube docardial region extends to within 1 to 2 mm of t lateral edge of the ischemic vascular bed; thus, in th region there is no lateral border zone of myocardiu salvageable by reperfusion.[3] In contrast, myocytes in t subepicardial region, where collateral blood flow greater, can be salvaged by reperfusion at 40 minute but will undergo infarction if the ischemia is allowed persist for ≥3 hours. Thus, the onset of irreversib ischemic cell injury does not occur simultaneously in a regions but develops as an expanding transmural wa front of cell death (Fig. 1).[3,4] Although there is no wa to prove this in man, it seems likely that a similar wa

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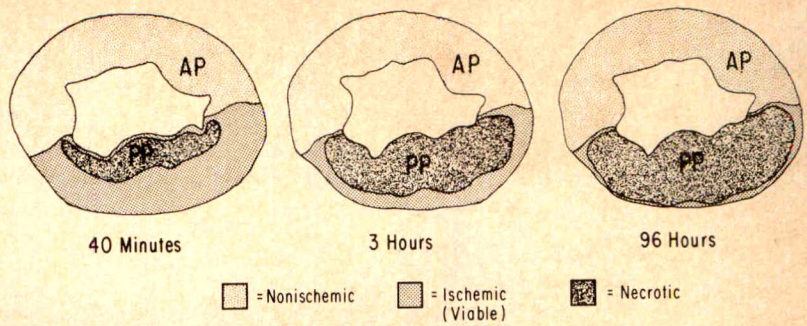

FIGURE 1. Progression of cell death versus time after occlusion of the circumflex artery in open-chest dogs. Necrosis occurs first in the subendocardial myocardium. With longer occlusions, a wave front of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. Thus, there is typically a large zone of subepicardial myocardium in the ischemic bed that is salvageable by early reperfusion but that dies in the absence of such an intervention. In contrast, the lateral margins in the subendocardial region of the infarct are established as early as 40 minutes after occlusion and are sharply defined by the anatomic boundaries of the ischemic bed. Reproduced from Reimer and Jennings[3] with permission of the publisher. AP = anterior; PP = posterior.

front of injury occurs after coronary occlusion in the human heart. In addition, the time course of cell injury in man only can be inferred from indirect indexes of ischemic injury. Nevertheless, animal data such as these provide a rational basis for early intervention in an evolving myocardial infarction and particularly for reperfusion through thrombolysis.

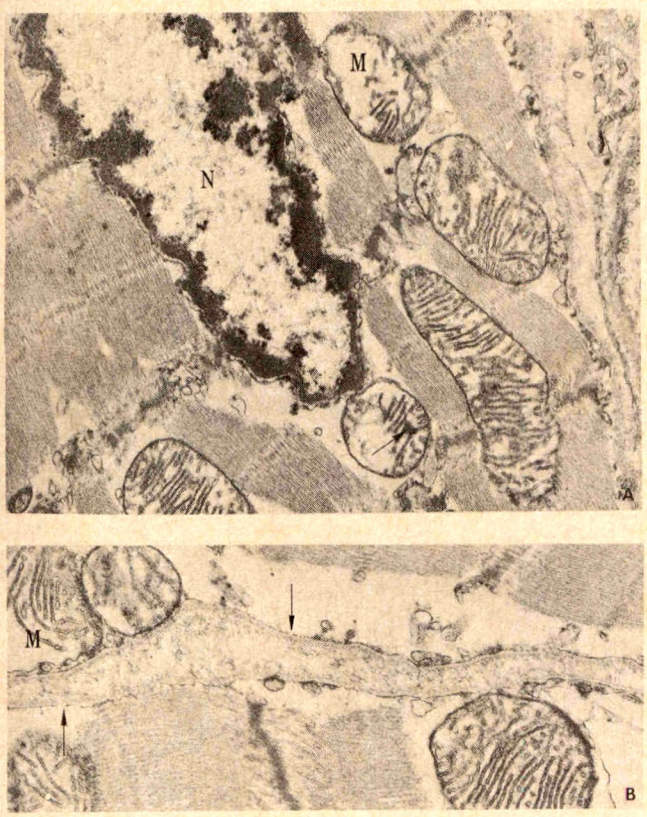

FIGURE 2. Posterior papillary muscle after 40 minutes of ischemia. **A,** the significant alterations from control include the marked margination of nuclear chromatin (N) and mitochondrial swelling (M) with the appearance of a clear matrix which often contains amorphous matrix densities (**arrow**). No glycogen is detectable. **B,** several small breaks are visible in the plasma membrane although the glycocalyx appears continuous. Swollen mitochondria (M) are present. The myofibrils are relaxed and show I bands. Original magnification: A ×31,000, B ×38,000; reduced 52%. Reproduced from Jennings et al[13] with permission of the publisher.

One of the major interests of our laboratory has been to characterize events associated with the transition from reversible to irreversible injury, with the aim of establishing the mechanism of ischemic cell death. To study this problem, we have confined our studies to the subendocardial region of severe ischemia and have compared myocardium reversibly injured by 15 minutes of ischemia with myocardium irreversibly injured by 40 minutes of ischemia.

Events During the Reversible Phase of Ischemic Injury

The onset of ischemia is accompanied by rapid changes in both myocardial metabolism and function.[5] Within the first 10 to 15 seconds after the occlusion, the tissue partial oxygen pressure decreases, mitochondrial respiration is inhibited, and the myocytes begin to use anaerobic glycolysis as the principal source of new high-energy phosphate (HEP). As a consequence, cellular glycogen levels decrease and lactate begins to accumulate in the ischemic tissue.

Contractile activity stops within 10 to 15 seconds of the onset of severe ischemia. Thus, ischemia induces an almost immediate effect on contractile function at a time when all myocytes still are viable and before much ATP depletion has occurred. Thus, loss of contractile function is not necessarily related to irreversibility. Severe ischemia is associated with the progressive loss of the cellular pool of HEPs, even though utilization of HEP by contractile activity is reduced or absent, for 2 reasons. First, anaerobic glycolysis can produce only 3 ATP molecules per glucosyl unit of glycogen converted to lactate, versus the 38 molecules of ATP produced with complete aerobic metabolism of glucose. In addition, after a brief burst of lactate production, the rate of anaerobic glycolysis is limited by end-product inhibition at ≥1 enzymatic steps. In part, the increasing lactate/pyruvate ratio slows the conversion of pyruvate to lactate so that the NADH/NAD (nicotinamide–adenine dinucleotide) ratio increases and glycolysis becomes inhibited at the glyceraldehyde-3-phosphate dehydrogenase level.[6] In addition, phosphofructokinase is inhibited by acidosis and high lactate concentrations.[7–9]

Thus, the metabolic consequences of severe ischemia result both from the reduction in substrate and oxygen

delivery and from the failure to remove end products of metabolism. In this regard, severe ischemia differs from hypoxia or mild ischemia. In the latter conditions, metabolites are removed from the tissue by continued perfusion. Because of this difference, the rate of anaerobic glycolysis is much faster in hypoxia with continued flow than it is in severe ischemia.[10,11]

Events Associated With the Onset of Irreversible Injury

We have identified several features of ischemic myocardium that are not present in reversibly injured myocytes, but which appear at about the time of the onset of irreversible injury[12]: (1) ATP is almost completely depleted.[13] (2) Mitochondria are swollen and contain amorphous matrix densities.[14] The latter are composed principally of lipid and perhaps contain protein; their functional significance and origin are uncertain.[15] (3) There is evidence of damage to the sarcolemma. Small breaks in the sarcolemma can be seen by electron microscopy.[13,16] Membrane defects also can be demonstrated in vitro by incubating slices of injured myocardium in an oxygenated Krebs-Ringer's phosphate medium. In such slices, intracellular components such as creatine are lost and the inulin-diffusible space expands, indicating increased membrane permeability to inulin.[17] Reperfusion of irreversibly injured cells in vivo results in explosive cell swelling of myocytes associated with massive influx of Ca^{++}.[18,19]

The ultrastructural characteristics of irreversible myocyte damage that are seen in severely ischemic myocardium 40 minutes after coronary occlusion in vivo are illustrated in Figure 2. Nuclear chromatin is clumped and mitochondria are swollen and contain amorphous matrix densities. In addition, small breaks are evident in the plasmalemma of the sarcolemma. These changes are characteristic of irreversibly injured myocardium, whether or not reperfusion has been established.

If the irreversibly injured myocardium is reperfused in vivo or reoxygenated in vitro, rapid changes occur which are termed explosive cell swelling[19] (Fig. 3). There are large subsarcolemmal blebs and the sarcolemma is severely damaged, often with areas in which scattered vesicles are the only remnants of the plasmalemma still attached to the glycocalyx. The severe membrane damage is associated with massive calcium overload.

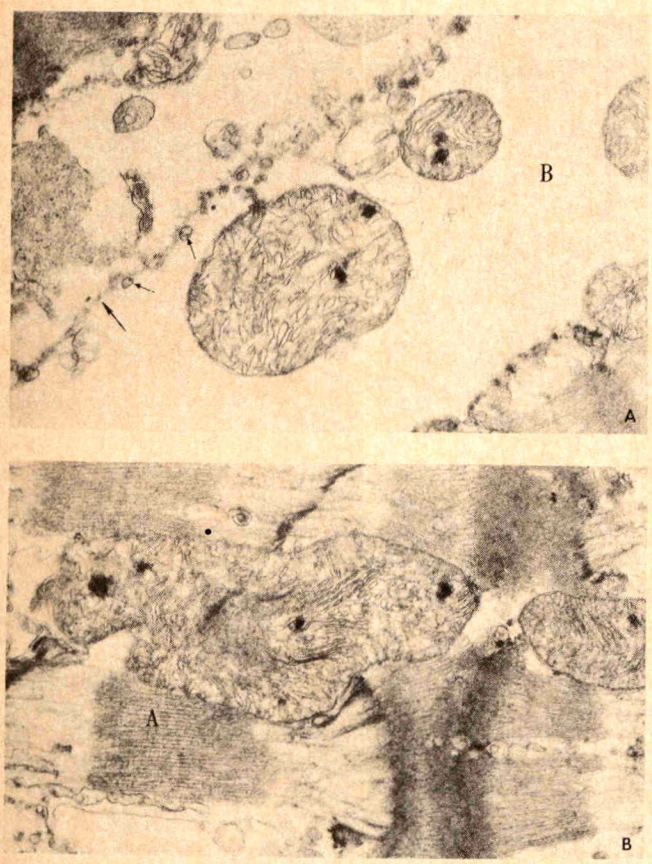

FIGURE 3. Posterior papillary muscle after 60 minutes of in vivo ischemia and 60 minutes of reoxygenation by slice incubation in vitro. **A,** a large subsarcolemmal bleb (B) that contains 2 mitochondria, each of which contains large, amorphous matrix densities. The remains of the sarcolemma show glycocalyx and circular profiles of plasma membrane (**arrows**). **B,** foci of hypercontraction of myofibrils. Two Z lines appear to be included in the aggregate at lower right, while an isolated A band (A) is seen at lower left between 2 superstretched I bands. A large mitochondrion contains several amorphous matrix densities. Original magnification: A and B ×28,000; reduced 52%. Reproduced from Jennings et al[13] with permission of the publisher.

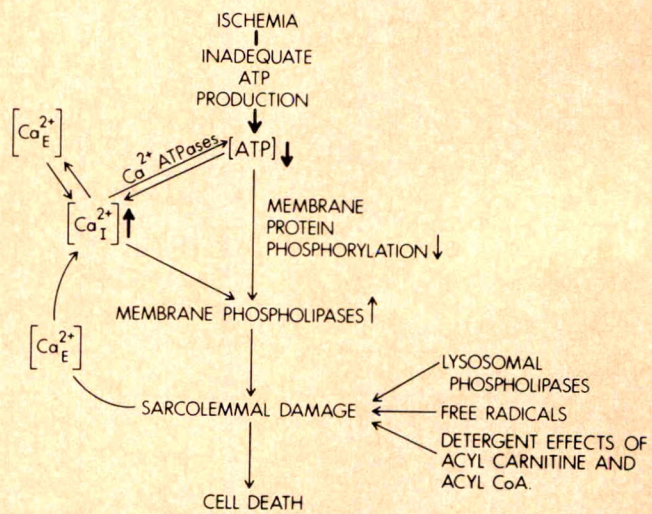

FIGURE 4. The potential relationships between ATP depletion, Ca^{++} influx, and sarcolemmal damage, which form the basis for various hypotheses of the events leading to sarcolemmal damage. The ATP of ischemic myocytes decreases because ATP utilization exceeds the capacity of anaerobic glycolysis to produce high-energy phosphates (HEP). Intracellular Ca^{++} (Ca^{2+}_i) may increase either because of increased membrane permeability to Ca^{++} or because of inadequate ATP to support the mechanisms responsible for Ca^{++} extrusion from the cell or sequestration of Ca^{++} by the sarcoplasmic reticulum. Increased Ca_i^{++} also may accelerate ATP depletion through Ca^{++} activated ATPases. Sarcolemmal damage occurs at ATP levels of 3 to 8% of control. The mechanism of damage is unknown. One explanation is activation of endogenous sarcolemmal phospholipases by the increased Ca_i^{++} or depressed phosphorylation of membrane proteins that ordinarily inhibit the activity of the endogenous phospholipases of the sarcolemma. Lysosomal phospholipase release, free radicals, or the detergent action of acyl carnitine or acyl coenzyme A also are possible causes of sarcolemmal damage in myocardial ischemia. Reproduced from Jennings and Reimer[12] with permission of the publisher.

Sarcomeres are supercontracted and the myofibrillar apparatus is disrupted with formation of contraction bands. Mitochondria accumulate some of the excess calcium, which is deposited as intramitochondrial crystalline densities.

Numerous hypotheses, which often are interrelated, have been proposed to explain the transition to irreversibility.[12] The most popular hypotheses focus on membrane damage (Fig. 4). The lethal event is considered to be disruption of the sarcolemma and perhaps other membrane systems of the cell; accordingly, the proximate cause of irreversibly would be the sequence of events that leads to functional and structural disruption of the membranes. The 2 major consequences of damage to the sarcolemma are the entry of excess Ca^{++} into the myocyte from the extracellular space, with resultant disruption of much of the internal metabolic machinery of the cell,[1,20] and the loss of critical intracellular components such as enzymes and cofactors through a leaky membrane to the extracellular space.[21] The causes of membrane disruption are unknown. Those proposed include activation of endogenous phospholipases of the sarcolemma as a consequence either of increased intracellular Ca^{++} [22] or of depressed phosphorylation of membrane proteins by the reduced sarcoplasmic ATP of the ischemic cell.[13] Alternatively, membranes could be damaged because of the action of phospholipases released from lysosomes, the detergent action of acyl carnitine and acyl coenzyme A, which accumulate in ischemia,[23] free radical effects such as lipoperoxidation,[24] or failure to resynthesize membranes lost through pinocytosis or other processes (turnover without replacement).

Mitochondrial defects also are a characteristic of the irreversible state and represent another potential cause of the transition to irreversibly.[15] Mitrochondrial function is inhibited in the absence of oxygen. Thus, mitochondrial damage would be of no added consequence as long as the tissue was severely ischemic. However, reoxygenation of ischemic myocardium must be followed by resumption of integrated mitochondrial function if the myocytes are to remain viable and recover contractile function.

Our working hypothesis is that cell death occurs when HEP (principally ATP) is depleted to levels insufficient to maintain the cell's structural integrity. Because HEP, in the form of ATP, is required for a large number of synthetic and degradative reactions within the cell, the premise that ATP is required to keep a cell functional and alive is generally accepted. However, the converse hypothesis, that the absence of HEP is the proximate cause of cell death, is unproved. The principal support for this hypothesis is circumstantial, that is, the close temporal relationship between HEP depletion and lethal myocardial ischemic injury.[13] This relationship will be described in more detail later. However, proof of this hypothesis will require the identification of ≥ 1 reactions that require ATP, the absence of which causes ischemic injury to become lethal. ATP is clearly essential for a wide variety of homeostatic mechanisms. In particular, ATP is essential for regulation of cellular Ca^{++} content and compartmentation.[21] In addition, low levels of sarcoplasmic ATP result in activation of phospholipases and depletion of mitochondrial adenine nucleotides causes the loss of phosphorylating capacity.[25] Alternatively, other metabolic consequences of ischemia unrelated to ATP depletion that could contribute to the cellular injury in ischemia include the accumulation of lactate or lactic acid[26,27] and acidosis.[28]

High-Energy Phosphate Production, Utilization and Depletion in Ischemia

Within seconds after the onset of severe ischemia, the available oxygen in the tissue is depleted and mitochondrial respiration is inhibited. Thereafter, any HEP utilized by the cell must come either from preexisting stores of ATP or creatine phosphate (CP) or from anaerobic glycolysis. Preexisting stores of HEP include 8 μmol of CP,[29] 5.8 μmol of ATP, and 1.2 μmol of ADP per gram of wet tissue weight. Because of the myokinase reaction, both HEP bonds at ATP can be utilized by the cell. Thus, the total preexisting store of HEP is about 20 μmol/g. Myocardium also contains about 44 μmol of glycosyl units of glycogen/g.[5] Each of these glucosyl

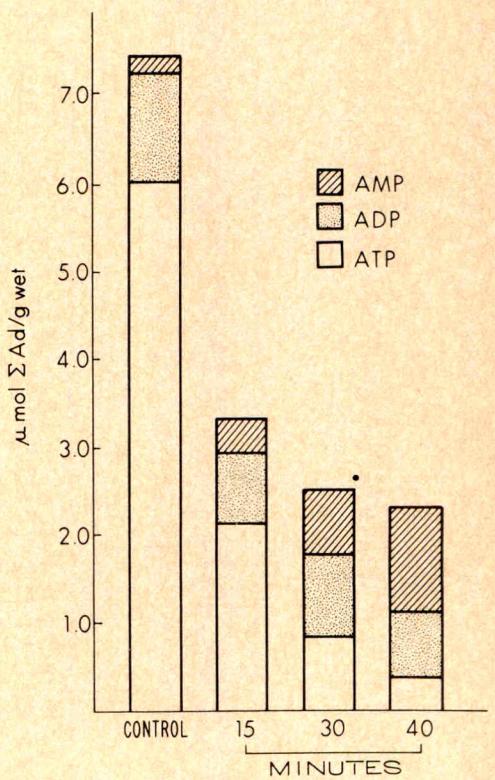

FIGURE 5. The adenine nucleotide contents of normal and severely ischemic myocardium of dogs subjected to proximal occlusion of the circumflex branch of the left coronary artery. Three to 5 dogs were used for each time point. Control data were pooled from all dogs. The ischemic tissue was obtained from the projecting portion of the posterior papillary muscle and the control nonischemic tissue came from the anterior papillary muscle. Intravenous thioflavine-S was used to identify the severely ischemic tissue and thereby exclude normal or mildly ischemic cells from the samples. After 40 minutes of ischemia, when most of the cells in this ischemic region are irreversibly injured, only 6% of the initial ATP remained and there was a 69% decrease in total adenine nucleotides. The data are plotted from Table 2 of Jennings et al.[13]

units can be metabolized to 2 μmol of lactate and, with the production of each micromole of lactate, 1.5 μmol of ATP are produced. If all the glycogen were consumed, 132 μmol/g of HEP could be produced. Thus, at the onset of ischemia, myocardium has a potential reserve of about 150 μmol of HEP/g.

ATP utilization is reduced markedly in ischemic myocardium because contractile function is suppressed. However, ATP continues to be consumed by various ATPases involved in the maintenance of cell volume and electrolyte gradients, in calcium homeostasis, and by other metabolic reactions. In severe ischemia, because the utilization of ATP always exceeds production, tissue levels decrease.[12]

The rapidity with which ATP is depleted from severely ischemic myocardium in vitro is illustrated in Figure 5. The ATP content decreases very rapidly to about 35% of control levels by 15 minutes (when the cells are still viable) and to <10% by 40 minutes (when the cells have been irreversibly injured).[13]

To study energy metabolism during ischemia in more detail, we also used a model of total ischemia in vitro.[5,17] Total ischemia is produced by excising normal hearts from dogs and simply keeping blocks of left ventricular myocardium in a moist environment at 37°C. In thi model, as in severe ischemia in vivo, there is progressiv depletion of ATP, parallel degradation of adenine nu cleotides, and accumulation of lactate (Fig. 6 and 7) The only difference is that these events occur mor slowly in vitro than in vivo.[5]

In both severe and total ischemia, the rate of lactat production was much less than the maximal rate tha could have been achieved if the end products of anaerobi glycolysis were washed out (Fig. 7). Nonetheless, gly colysis provided about 80% of the HEP utilized by th totally ischemic myocardium during the first 90 min utes. Thereafter, lactate production virtually stopped This occurred when only 50 to 60 μmol/g of lactate hac accumulated, that is, much less than the 88 μmol/g ex pected from the complete utilization of the glycoger known to be present in the tissue. This complete inhi bition of lactate accumulation followed the virtua complete depletion of ATP.

Possible explanations for the inhibition of anaerobi glycolysis late in ischemia include degradation o washout of cofactors such as NAD, or the inactivatio or inhibition of ≥1 enzymes of the glycolytic scheme Lack of substrate is an unlikely explanation becaus

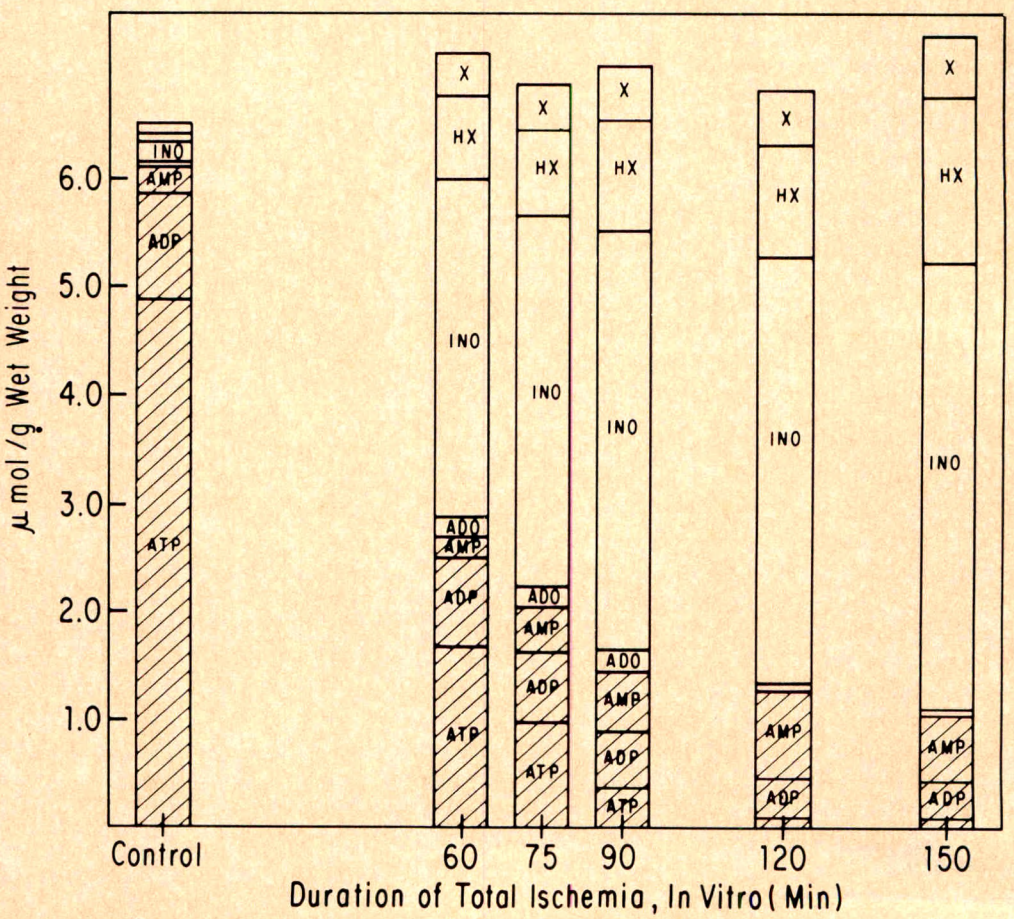

FIGURE 6. The decrease in ATP, ADP and ΣAd (ATP, ADP, plus AMP) that occurs as a function of the period of total ischemia. The decrease in the ΣAd was accounted for by a marked increase in the content of inosine (INO), hypoxanthine (HX), and xanthine (X). Reproduced from Jennings et al[5] with permission of the publisher.

glycolysis ceased even though some glycogen and a significant amount of glucose-6-phosphate remained in the tissue. The concurrence of severe ATP depletion and cessation of lactate production suggests that depletion of ATP levels below that required to phosphorylate fructose-6-phosphate to fructose-1,6-diphosphate is the most likely explanation for inhibition of anaerobic glycolysis.

ATP Depletion Versus Signs of Sarcolemmal Damage

Other signs of the onset of irreversible injury appear at or after the virtual depletion of ATP. For example, the relation between the ATP content of totally ischemic myocardium and the capacity of slices of this injured tissue to exclude inulin or to retain creatine is illustrated in Figure 8. We consider an increased IDS and decreased creatine content to be signs of increased membrane permeability, and, when marked, to be objective evidence of cell death. This evidence of membrane damage did not develop in any slice with a starting ATP >2.0 μmol/g. Thus, cell death is preceded by the cessation of energy utilization occasioned both by loss of HEP stores and inhibition of further HEP production through anaerobic glycolysis. A similar association between ATP depletion and increased membrane permeability to trypan blue has been observed in anoxic isolated rat heart myocytes.[29]

Structural Recovery Versus Slow Repletion of ATP After Brief Periods of Ischemia (Reversible Injury)

As noted earlier, 15 minutes of severe ischemia causes reversible injury in the sense that reperfusion will prevent the death of the ischemic cells and will restore the slight alterations in ultrastructure toward normal.[19] We have compared the ultrastructural appearance of myocardium that had been made severely ischemic for 15 minutes and then was reperfused for 24 hours with nonischemic myocardium from the same hearts. Figures 9 and 10 show representative changes seen among hearts from 4 dogs studied at this time interval; Figure 10 demonstrates the most severe changes found. No persistent cellular damage was observed. Nuclei and myofibrils were normal in both ischemic-reperfused and

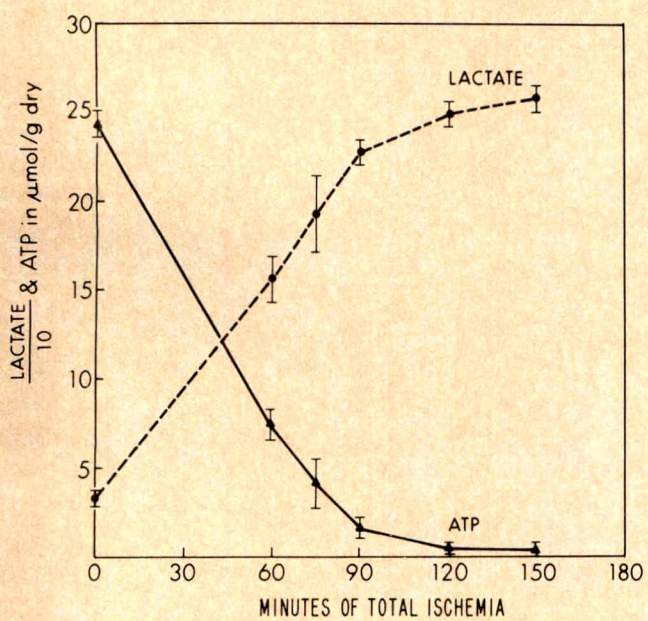

FIGURE 7. The ATP and lactate content of papillary muscles of dog hearts after varying periods of total ischemia. The hearts were quickly removed from the anesthetized dogs. Both left ventricular papillary muscles were excised quickly and, after obtaining control samples, were incubated at 37°C in a moist environment. The results are reported on the basis of dry weight, but can be divided by 5 to provide approximate results on the basis of wet weight for comparison with other studies illustrated in this paper. ATP degradation and lactate production ceased almost simultaneously at 90 minutes. The results are the mean of 4 to 6 animals at each point. The **bars** represent the standard error of the mean. Reproduced from Reimer et al[17] with permission of the publisher.

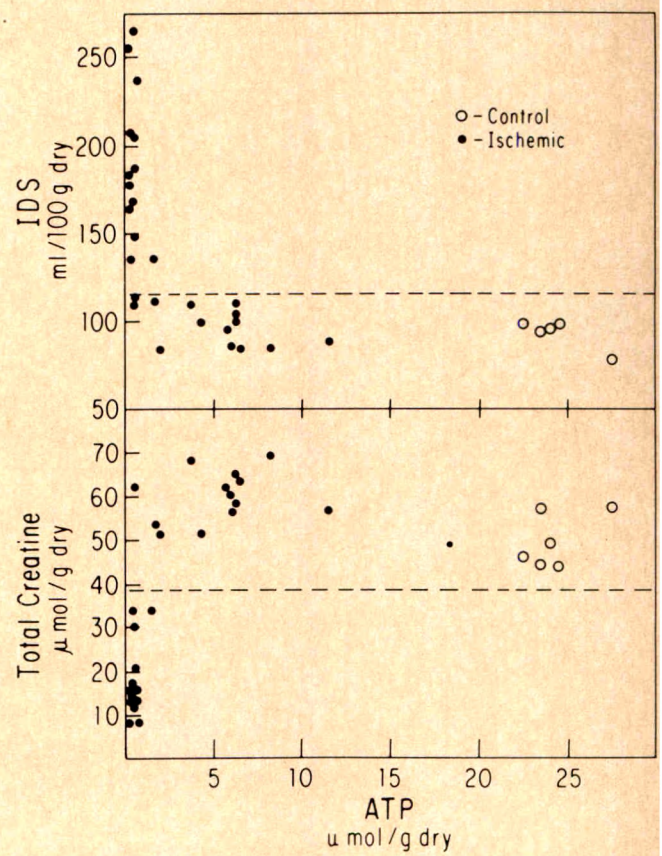

FIGURE 8. The capacity of control or injured slices to exclude inulin or retain creatine compared with the ATP content of the tissue before incubation. The **dashed lines** mark 2 standard deviations above and below the control mean inulin-diffusible space (IDS) and total creatine content, respectively. The data are plotted irrespective of the duration of total ischemia. Overt membrane damage, as indicated by increased permeability to these 2 markers, did not develop until the tissue ATP content was <2.0 μmol/g dry weight. Thus, overt membrane damage was manifest later than the defective regeneration of high-energy phosphates HEP. Reproduced from Reimer et al[17] with permission of the publisher.

nonischemic regions and no sarcoplasmic edema or vacuolization were detected. Most mitochondria also were normal. Occasional mitochondria from both ischemic reperfused and nonischemic regions showed slight swelling and a few mitochondria were enveloped by lysosomes. Such changes may be artifacts of tissue sampling or may be indicative of focal mitochondrial injury and increased turnover. Occasional perinuclear filamentous bodies of unknown origin also were seen in the ischemic-reperfused and occasionally in the nonischemic regions. In short, the similarity of ultrastructural findings in ischemic-reperfused and nonischemic regions indicate that 24 hours after reversible ischem injury, cardiac myocytes are structurally indistir guishable from control.

The data in Figure 5 show that although the injur is structurally reversible, 15 minutes of severe ischemi results in a 65% decrease in ATP.[13] In addition, th progressive reduction in tissue ATP content is para leled by destruction of the adenine nucleotides. Th major pathways of adenine nucleotide metabolism[30–3 are shown in Figure 11. The HEP bond remaining in th ADP molecule can be recovered by the myokinas (adenylate kinase) reaction, in which 1 ATP and adenosine monophosphate (AMP) molecule are pro duced from 2 ADP molecules. The resulting ATP i utilized and the remaining phosphate of AMP is cleave irreversibly by 5′-nucleotidase, resulting in adenosin and inorganic phosphate. The adenosine produce leaves the myocyte. Adenosine is a potent vasodilato this metabolic pathway may be responsible for th feedback control of myocardial blood flow. However, i the presence of continued severe ischemia, this step i responsible for the depletion of the cellular pool of ad enine nucleotides. The adenosine produced quickly i deaminated to inosine, the ribose moiety is cleaved t produce hypoxanthine, and a small amount of xanthin is produced as well.

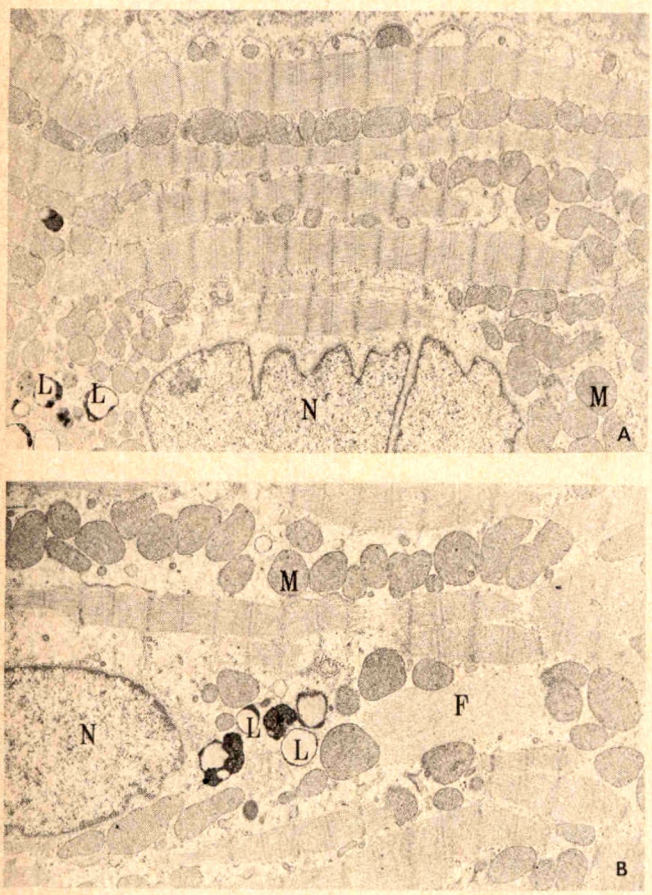

FIGURE 9. Nonischemic myocardium (**A**) from the anterior papillary muscle compared with myocardium from the posterior papillary muscle (**B**), which had been made severely ischemic by 15 minutes of circumflex artery occlusion and then was reperfused for 24 hours. The area of previous ischemia was identified by reoccluding the circumflex artery 15 seconds before excising the heart and injecting thioflavin-S intravenously. The posterior papillary samples were taken from the center of the nonfluorescent region of severe ischemia. Fixation was by immersion in 4% glutaraldehyde with postosmication. These illustrations are representative of findings among 4 dogs studied under these conditions. No striking differences between nonischemic and ischemic regions were observed. The nuclear (N) chromatin is evenly distributed, mitochondria (M) are abundant and generally have tightly packed cristae, and lysosomes (L) are intact. The myofibrils also are indistinguishable in the 2 regions. Neither contraction bands nor persistent relaxation were identified in any of the 4 dogs. A perinuclear filamentous body (F) of unidentified origin is present in B. Although not seen in the nonischemic region of this heart, similar structures were seen in both the nonischemic and ischemic samples of 2 of the other hearts. Original magnification: A ×10,400, B ×11,500; reduced 45%.

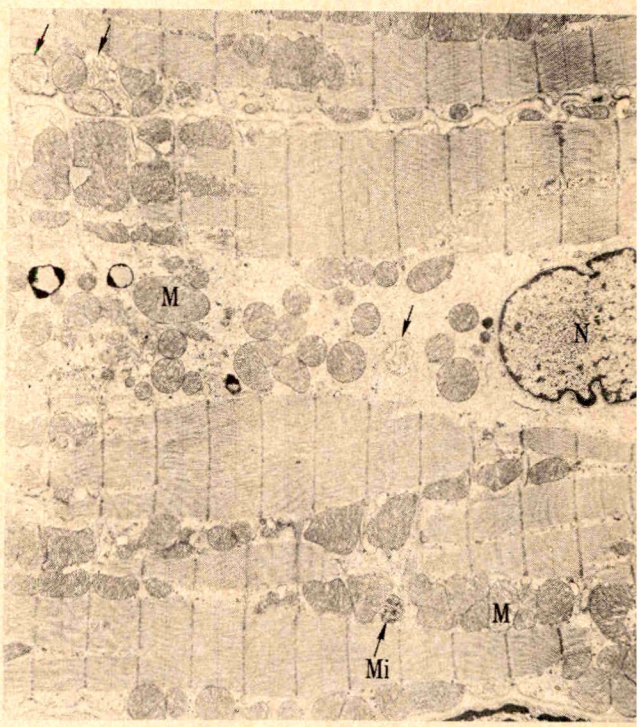

FIGURE 10. Myocardium after 15 minutes of circumflex occlusion an 24 hours of reperfusion (same experimental conditions as describe in Figure 9). This illustration is representative of the most marke changes seen in the previously ischemic region. The overall architecture is intact. However, a few mitochondria are swollen (**arrows**) and 1 mi tochondrion (Mi) contains amorphous matrix densities. The remaining mitochondria (M) are indistinguishable from control, as are the myofi brils, nuclei, sarcoplasm, sarcolemma and sarcoplasmic reticulum Original magnification ×9,675; reduced 47%.

Since the amount of the decrease in the adenine nucleotide pool was unexpectedly large in ischemia, we assessed the rate of net ATP and adenine nucleotide repletion after 15 minutes of severe in vivo ischemia, that is, late reversible injury.[33] The adenine nucleotide content of nonischemic and ischemic myocardium after 15 minutes of coronary occlusion is shown in Figure 12. The nonischemic nucleotide contents were similar to those measured in other laboratories.[29] By 15 minutes of coronary occlusion there was a 60% loss of ATP. ADP content was also slightly decreased. AMP was significantly increased, but this increase was quantitatively small compared with the ATP loss. Thus, total adenine nucleotides were reduced by 50%.

The effect that various periods of reperfusion after 15 minutes of ischemia had on tissue ATP content is shown in Figures 13 and 14. The ATP content of nonischemic myocardium was similar at all times studied. In the ischemic region, the ATP content increased slightly but significantly after 20 minutes of reperfusion. This early recovery of ATP is probably due to the recharging of the ADP and AMP remaining after the period of ischemia. However, no further increase in ATP content was detected even at 24 hours. By 4 days, the ATP level appoached, but still was significantly less than, the control level of ATP. This slow recovery of ATP content was paralleled by, and probably due to, the

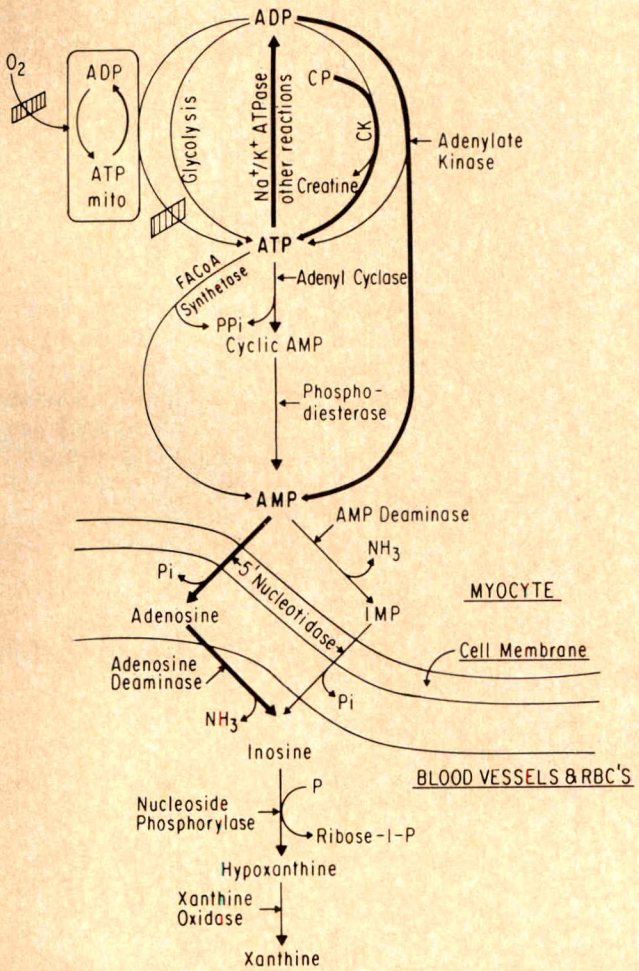

FIGURE 11. The major metabolic pathways of adenine nucleotide degradation during myocardial ischemia. The most quantitatively important pathways are indicated by the **solid thick arrows.** See text for further explanation. Reproduced from Jennings et al[5] with permission of the publisher. CP = creatine phosphate; ADP = adenosine phosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.

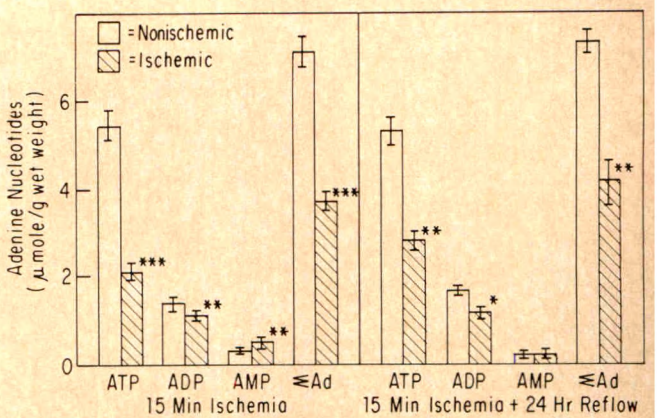

FIGURE 12. The effects of 15 minutes of ischemia without reperfusion (**left**) and with 24 hours of reperfusion (**right**) on total adenine nucleotides. After ischemia, ATP was reduced 60%. ADP was also reduced and although AMP was increased, the total adenine nucleotide content was decreased 50%. Nonischemic and ischemic samples from each dog were compared by paired *t* statistical analysis. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Reprinted from Reimer et al[33] with permission of the publisher.

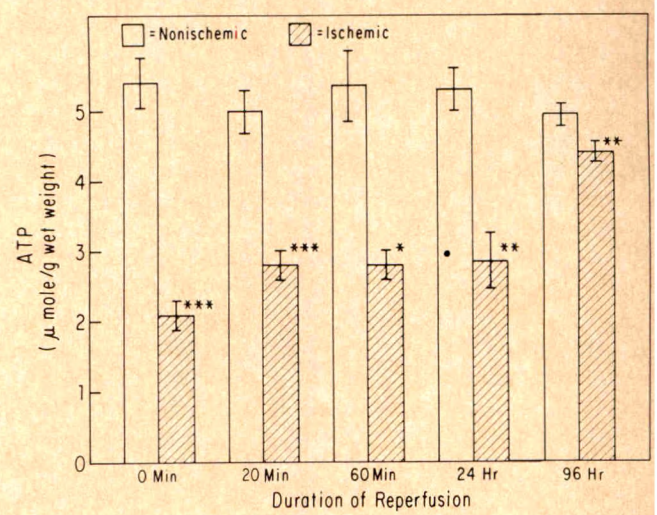

FIGURE 13. The effects of 15 minutes of ischemia with 0, 20 or 60 minutes and 24 or 96 hours of reperfusion of ATP content. ATP was markedly reduced in ischemic samples at all 5 times studied. ATP content increased slightly during the first 15 minutes of reperfusion, most likely because of rephosphorylation of ADP and AMP. ATP content showed no additional increase over the next 24 hours and was still slightly decreased at 96 hours. Brackets indicate the standard error of the mean. Nonischemic and ischemic samples from each dog were compared by paired *t* statistical analysis. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Comparison between groups using a nonpaired *t* test showed significant increases in ATP with all times of reperfusion compared with no reperfusion ($p < 0.05$). **Open bars,** nonischemic; **hatched bars,** ischemic samples. Reproduced from Reimer et al[33] with permission of the publisher.

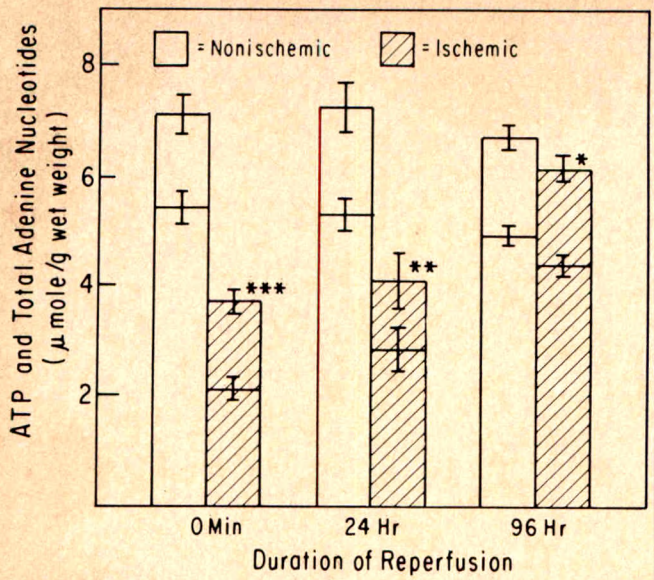

FIGURE 14. The effects of 15 minutes of ischemia and 0, 24, and 96 hours of reperfusion on total adenine nucleotide content. The total adenine nucleotide pool was still markedly reduced after 24 hours of reperfusion. By 96 hours, adenine nucleotide content had returned almost to normal, but was still significantly reduced compared with ischemic samples from the same hearts. The proportion of total adenine nucleotides in the form of ATP (from Figure 2) is indicated on each bar. Brackets indicate ± standard error of the mean. Nonischemic and ischemic samples from each dog were compared by paired *t* analysis. * $p < 0.05$, ** $p < 0.001$. Reproduced from Reimer et al[33] with permission of the publisher.

slow repletion of the total adenine nucleotide pool (Fig. 14). Both salvage and de novo pathways of adenine nucleotide synthesis are known to be slow in myocardium.[34,35]

These results have at least 2 major implications: (1) The delayed resynthesis of ATP may explain the slow functional recovery after brief periods of ischemia in experimental animals.[33,36–38] To the extent that the results are applicable to man, delayed resynthesis of adenine nucleotides may be one explanation why cardiac function often recovers slowly after cardiac surgery despite bypass of obstructed coronary arteries. (2) Repeated brief episodes of ischemia should have a cumulative effect on tissue ATP content. Thus, repeated episodes of angina probably have cumulative effects on the adenine nucleotide content of the affected myocardium, with possible functional consequences.

A variety of approaches have been tried with the aim of enhancing repletion of adenine nucleotides. Reibel and Rovetto[39] attempted without success to enhance postanoxic ATP regeneration in isolated perfused rat hearts either with ATP or adenosine. The explanation for their results may lie in the relative impermeability of the sarcolemma to ATP and the rapid catabolism of adenosine by way of the adenosine deaminase pathway. To overcome the latter problem, Foker et al[40] achieved enhanced recovery of ATP levels in ischemic dog hearts by combining adenosine with erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride, an inhibitor of adenosine deaminase. Alternatively, Zimmer et al[41] showed that the rate-limiting step for either de novo or salvage synthesis of adenine nucleotides is the formation of phosphoribosyl-1-pyrophosphate in the hexose monophosphate shunt. By enhancing this pathway by providing ribose, adenine nucleotide synthesis has been enhanced in rats in which myocardial ATP had been depleted by isoproterenol or asphyxia.[42,43]

In conclusion, myocardial ischemia is associated with the progressive depletion of HEP and the adenine nucleotide pool. In the subendocardial region of severe ischemia, ATP content is reduced to <10% of control levels by 40 minutes of ischemia in vivo; this marked depletion of ATP coincides with the onset of cell death. Cell death is completed in this region by the time 6 minutes has elapsed.

The subepicardial region often receives more collateral blood flow, and cell death in this region may be delayed for 3 to 6 hours. Thus, there is a transmural wave front of cell death in myocardial ischemia. Successful intervention to protect ischemic myocardium should be expected to limit the transmural extent of a infarct and transform a potentially transmural infarct into a subendocardial one.

Modest depletion of ATP due to brief periods of transient ischemia may not result in cell death, but there may be partial depletion of the adenine nucleotide pool. Even though reperfusion is established, the slow repletion of this pool may prevent early recovery of HEP content, and thus may be responsible for prolonged depression of contractile function. This concept of prolonged functional depression despite reversible cellular injury may be important in a number of settings including cardiac depression after cardiac surgery, cardiac failure in patients with angina pectoris, and evaluation of the effects of thrombolytic agents in the early therapy of acute myocardial infarction. Since the long-term effects of reperfusion may not be immediately evident, evaluation several days later might provide a better end point to judge the outcome of thrombolytic therapy. Whether acceleration of the pathways for adenine nucleotide synthesis facilitates functional recovery in the situations mentioned earlier remains to be established.

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Prognostic Value of Submaximal Exercise Radionuclide Ventriculography After Myocardial Infarction

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Submaximal exercise testing with radionuclide ventriculography (RVG) was performed in 117 patients before hospital discharge 17 ± 7 days (± standard deviation) after an acute myocardial infarction (MI). The hypothesis tested in these studies was that submaximal exercise testing coupled to RVG allows the identification of patients at risk for future ischemic events in the subsequent 6 months, irrespective of MI location and type. The sites of MI were characterized as anterior transmural in 33, inferior transmural in 39, limited nontransmural in 18, extensive nontransmural in 24 and indeterminant in 3. During 6 months of follow-up, 9 patients died, 14 had recurrent MI, 18 had refractory angina pectoris, 16 had limiting angina and 17 had congestive heart failure.

Discriminant function analysis ranked exercise changes in left ventricular (LV) ejection fraction and end-systolic volume the most important of all clinical, exercise and scintigraphic variables for predicting future cardiac events. The predictive accuracy of changes in LV ejection fraction and end-systolic volume were 93 and 91%, respectively, for the entire group, and were significantly more sensitive than any degree of ST-segment depression or elevation ($p < 0.001$). These findings were generally independent of MI location and type. Thus, submaximal exercise RVG after MI is an accurate means of identifying patients at risk for major cardiac events in the 6 months after hospital discharge.

An unfavorable prognosis after a myocardial infarction (MI) has been related to large infarct size, significant left ventricular (LV) dysfunction, anterior location of the MI, the transmural or nontransmural extent of the injury, and a prior MI.[1–13] When coupled with prior damage, an acute MI need not be large to result in a fatal outcome.[14] The extent and severity of coronary arterial stenoses and the functional state of the noninfarcted left ventricle also have been correlated with patient survival.[15,16] Therefore, the identification of the extent of damaged myocardium and "myocardium at risk" should provide prognostic information.[17,18] Radionuclide ventriculography (RVG) is an established noninvasive technique for measuring LV function.[19,20] Submaximal exercise testing with electrocardiography after MI provides prognostic information, presumably indicating "myocardium at risk."[18,21–25] In this study, we tested the hypothesis that submaximal exercise testing with RVG in patients after MI allows one to predict prognosis independent of the location or type of the MI.

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Methods

Patients: All patients admitted to the coronary care unit of Parkland Memorial Hospital from August 1978 to January 1981 in whom a diagnosis of acute MI was made were considered for study. The 117 patients in this report represent approximately 50% of patients with acute MI admitted during this period. Patients with unstable angina after MI, severe congestive heart failure, musculoskeletal disorders impairing their ability to exercise, participation in other research protocols which might alter the results of exercise testing, or who refused to provide informed consent were excluded. Age, sex, systemic arterial hypertension (>180/100 mm Hg), therapy with digoxin, beta blockers or antiarrhythmics, and electrocardiographic abnormalities complicating interpretation of the ST segments were not considered reasons for exclusion. We obtained submaximal exercise tests with scintigraphy before hospital discharge to detect serious arrhythmias and severe myocardial ischemia developing with mild to moderate effort.[18,26,27]

TABLE I Clinical Characteristics (n = 117)

Age (yr)	25–80 (mean 53)
Men	78
Women	39
History of MI	36
Killip class III	14
Anterior TM MI	33
Inferior TM MI	39
Limited NT MI	18
Extensive NT MI	24
Cardiac medications at SE ETT	93

MI = myocardial infarction; NT = nontransmural; SE ETT = submaximal exercise tolerance test; TM = transmural.

The study population consisted of 116 patients in whom sufficient follow-up information to assess clinical course and subsequent cardiac events was available for at least 6 months after MI (Table I). One additional patient was lost to follow-up after 3 months.

There were 78 men and 39 women with a mean age of 53 years (range 25 to 80). Thirty-six patients had a previous MI. The diagnosis of acute MI was based on electrocardiographic,[18] enzymatic (creatine kinase [CK] and CK-B isoenzyme),[28] and technetium-99m stannous pyrophosphate myocardial scintigraphic criteria.[29] Anterior MI was defined by the development of new Q waves, ST-T-wave changes or ≥50% loss in R-wave voltage in leads I, aVL, or V_1 to V_6. Inferior (or true posterior) MI was defined by similar changes in leads II, III and aVF or the development of R > S-wave amplitude in precordial leads V_1 and V_2. Transmural MI in all locations was diagnosed by the development of Q waves ≥0.04 second in duration, a Q ≥ 25% of R-wave amplitude, or a ≥50% loss in R-wave voltage.[30] Nontransmural (subendocardial) MI was recognized by the presence of ST- and T-wave abnormalities without the development of significant Q waves or R-wave loss. Using these criteria, 72 patients had transmural MI: 33 anterior and 39 inferior. Because of difficulties in accurately localizing nontransmural MI by the electrocardiogram, nontransmural MI changes limited to ≤4 of the precordial leads and leads I and aVL or only leads II, III, and aVF were classified as "limited nontransmural," and those that involved more leads were classified as "extensive nontransmural."[31] Forty-two patients had nontransmural MI, 18 limited and 24 extensive. Three patients had left bundle branch block and were classified as having an MI of indeterminant location and type.

Exercise testing: Exercise tests were conducted a mean of 17 ± 7 days (± standard deviation [SD]) after MI and were performed generally 1 or 2 days before hospital discharge. No attempt was made to alter medical therapy before exercise testing. Drug therapy at the time of testing consisted of digoxin (32 patients), propranolol (29 patients), long-acting nitrates (53 patients), and antiarrhythmic agents (36 patients). No patient had taken nitroglycerin for chest pain within 48 hours of testing. Exercise testing was performed in the supine feet-up position with a bicycle ergometer.[18] The Frank lead system[32] was used to monitor the electrocardiographic responses continuously during exercise in 75 patients and a standard 12-lead system was used in 43. Horizontal or downsloping ST-segment depression ≥0.05 mV or ST elevation ≥0.1 mV with the Frank lead system were considered indicative of ischemia.[33,34]

Blood pressures (by sphygmomanometer) at rest and near the completion of each exercise level were recorded. Graded exercise was performed beginning at 150 or 300 kpm and was increased by 150 to 300 kpm at each subsequent exercise level, depending on age, body habitus and performance at the earlier exercise levels. The duration of exercise was approximately 4 minutes at each work load. Exercise was continued until a target heart rate of 130 beats/min was achieved or one of the following endpoints was reached: (1) progressive chest discomfort compatible with angina pectoris, (2) complex ventricular arrhythmias,[35] (3) ST-segment depression of ≥0.2 mV compared with resting morphology, (4) decreasing systemic arterial blood pressure, or (5) incapacitating fatigue or dyspnea. Patients who developed angina or ST-segment displacement were allowed to complete the current exercise level whenever possible in order to complete scintigraphic data collection.

Radionuclide technique and imaging protocol: Multigated equilibrium blood pool imaging was performed after in vivo labeling of red blood cells with 30 mCi of technetium-99m sodium pertechnetate according to a standard technique.[26] Data collection was performed with a standard gamma scintillation camera (Ohio Nuclear Series 100) equipped with an all-purpose, parallel-hole collimator and interfaced with a dedicated on-line computer system (Ohio Nuclear VIP-450). Resting equilibrium gated blood pool scintigrams were obtained in multiple projections, including a modified 25 to 50° left anterior oblique projection as required for best septal definition and left ventricular isolation.

Scintigrams at rest and during submaximal exercise were acquired for a preselected time interval of 2 to 3 minutes and 90 to 100% of the cardiac cycle. Thirty-two frames/cycle with 75,000 to 150,000 counts/frame were acquired. Imaging began at each work load after the completion of 1 minute of exercise, which allowed the heart rate to stabilize and uninterrupted gating to proceed. At each work load during exercise, heart rate did not vary by >10% of the value recorded at the start of scintigraphic data collection.

Analysis of radionuclide ventriculograms: LV ejection fraction was calculated by a standard technique using the background-corrected activity from the regions of interest constructed over the ventricle at end-diastole and end-systole.[19] LV volumes were calculated by a nongeometric technique developed and validated by Dehmer et al[20,36] in our laboratory as well as by others. With this technique, LV volumes are calculated from the LV activity normalized for counts per milliliter of peripheral venous blood and acquisition time per frame. The arterial systolic blood pressure and LV end-systolic volume index (P/V index) was calculated by dividing the cuff-determined systolic blood pressure by LV end-systolic volume corrected for body surface area.[37]

A subjective analysis of LV segmental wall motion was obtained using a cinematic display of the entire cardiac cycle as well as a 2-frame display of end-diastole and end-systole. The LV was divided into 5 segments and each was graded according to the following scale: 4 = normokinesia, 3 = hypokinesia, 2 = severe hypokinesia, 1 = akinesia and 0 = dyskinesia.[18] The scores for all segments were summed at rest and at each exercise level, respectively, and the results are reported as a percentage of the maximal possible score.

Scintigraphic variables: The following measurements of LV function were evaluated for their ability to identify patients at risk for subsequent cardiac events: a resting LV ejection fraction <0.40, failure of the LV ejection fraction to increase by ≥0.05 during exercise, failure of the P/V index to increase by 35% during exercise, a >5% increase in LV end-systolic volume index during exercise, and a decrease in wall motion score during exercise.[37] An initial increase in LV ejection fraction with a subsequent decrease of ≥0.05 was considered significant even if the peak submaximal value was 0.05 greater than the resting value. Maintenance with exercise

TABLE II Clinical and Exercise Variable Correlates With Cardiac Events by 6-Month Follow-Up

	No Cardiac Events (n = 43)	p value	Cardiac Events (n = 74)
Age (yr)	49 ± 13	NS	56 ± 11
Sex (M/F)	35/8	0.014*	43/31
History of MI	6	0.003	30
Killip class III	2	0.079	12
Chest pain with SE ETT	3	NS	12
Complex ventricular arrhythmias	3	NS	5
Anterior TM	6	0.01	27
Inferior TM	18	NS	21
Limited NT	10	NS	8
Extensive NT	9	NS	15
Indeterminant	0	NS	3

* The incidence of cardiac events in female patients, not significant in males.

MI = myocardial infarction; NS = not significant; NT = nontransmural; SE ETT = submaximal exercise tolerance test; ST = ST segment; TM = transmural.

TABLE III Submaximal Exercise Test Characteristics*

	No Cardiac Events (n = 43)	p value	Cardiac Events (n = 74)
Maximal blood pressure (mm Hg)	180 ± 28	NS	163 ± 32
Maximal heart rate (beats/min)	116 ± 19	NS	113 ± 17
Maximum work load (kpm)	373 ± 195	<0.01	229 ± 109
Exercise chest discomfort	3	NS	12
ST changes†	21	<0.05	57
ST depression (0.1 mV)	9	NS	25
Exercise arrhythmias	3	NS	5

* Patients classified according to 6-month follow-up.
† 0.05 mV ST depression or 0.1 mV ST elevation.
NS = not significant.

of a resting LV ejection fraction ≥0.75 or a <0.05 increase were also considered normal responses.

Follow-up: The clinical course and hospital records of all patients were reviewed. Eighty-three patients were seen and examined by 1 of the investigators during the follow-up period. The hospital and clinic records of 20 patients cared for by other physicians at this institution were reviewed. Twelve patients and the immediate family of 6 patients (5 of whom had died) were interviewed by telephone. The mean follow-up period for all patients was 8.3 ± 5.1 months. Those who had no subsequent cardiac events were followed for 9.4 months (range 6 to 20), whereas those with subsequent cardiac events were followed for 7.3 months (range 1 to 24). Thirty-two patients with and 24 patients without subsequent cardiac events were followed for >6 months. We did not attempt to withhold or restrict medical therapy. For the purposes of this study, the following were considered important cardiac events: sudden death, cardiac death, recurrent myocardial infarction, episodes of unstable angina and medically refractory angina resulting in surgical intervention (hereafter referred to as "medically refractory angina"), persistent congestive heart failure, including episodes of pulmonary edema or persistent physical examination and radiographic evidence of congestive heart failure or both, and classic angina pectoris believed to interfere with preinfarction lifestyle ("limiting angina"). Death, recurrent MI and medically refractory angina were considered major cardiac events, whereas the others were considered minor events. Adequate follow-up was available on all patients at 6 months, with the single exception mentioned earlier. Follow-up was discontinued in patients who had coronary artery bypass surgery.

Statistical methods: Group comparisons of continuous variables are reported as the mean ± 1 SD. The analysis of intergroup differences was performed using a 1-way analysis of variance[38] and the appropriate multiple-range test for the continuous variables of interest.[39] Similarly, differences among groups in categorical variables were analyzed using Fisher's exact test[38] for equality of group proportions. McNemar's test[38] was used to compare the sensitivities of any 2 diagnostic techniques.

Stepwise discriminant analyses[40] were performed to assess the degree to which the clinical, exercise and RVG variables predicted the occurrence of subsequent cardiac events at 3- and 6-month follow-up. At each of the 2 follow-up periods, the patients were classified into 1 of 4 groups, based on the presence or absence of cardiac events: (1) no cardiac event; (2) any cardiac event; (3) minor cardiac event; and (4) ≥1 major cardiac event. In the discriminant analysis procedure, linear combinations of the predictor variables, called "classification functions," were obtained for the purposes of predicting group membership. The stepwise procedure enters these variables into the analysis successively on the basis of their discriminating power. At each stage of the procedure, the ability of the variables currently in the analysis to classify correctly the patients into the different groups is evaluated by determining the proportion of patients which are classified correctly. To adjust for possible bias, a "jack knife" validation procedure[40] was used which, in essence, classifies each of the current patients on the basis of a classification function that involves only the other patients in the study. Therefore, the discriminant analysis evaluation and the modification of this evaluation using the jack-knife procedure represent an attempt to classify patients using the variables described without influencing the classification results from this specific patient population.

Results

Clinical characteristics: There was no significant difference in age between patients with or without subsequent cardiac events. Female patients had a greater incidence of cardiac events (p = 0.014) (Table II). Patients with a history of MI also had a greater incidence of cardiac events (p = 0.003). Submaximal exercise-induced chest pain, ST depression of ≥0.1 mV and complex ventricular arrhythmias were not significant in distinguishing patients with cardiac events. ST-segment changes (depression ≥0.05 mV or elevation of ≥0.1 mV or both) were significant in predicting cardiac events (p = 0.002).

Clinical outcome: Seventy-four patients (63% of the study population) had at least 1 cardiac event during the 6-month follow-up. Nine of the 117 patients (8%) died (5 suddenly), 14 (12%) had recurrent MI and 18 (15%) had medically refractory or unstable angina that led to surgical intervention. Seventeen patients (15%) developed congestive heart failure and 16 (14%) had limiting angina despite medical therapy (Table III).

After 3 months of follow-up, cardiac events had occurred in 65 of the 74 patients who were to have events

within 6 months of follow-up. There was a tendency to progress from minor to major cardiac events over time; the number of patients with major cardiac events increased from 28 at 3 months to 41 at 6 months.

Bicycle exercise test and electrocardiographic results: No complications resulted from submaximal exercise testing in these patients. There were no significant differences in the maximal heart rate and blood pressure between patients with and without cardiac events, (Table III). The maximal work load performed was significantly greater in the patients without cardiac events (373 ± 195 versus 229 ± 109 kpm, $p < 0.01$).

Fifteen patients had chest pain and 78 patients had ≥0.05 mV ST depression or ≥0.1 mV ST elevation with submaximal exercise or both. Thirty-four of the 78 patients with ST changes had ≥0.1 mV of ST depression. The incidence of ST-segment depression of ≥0.05 mV or elevation ≥0.1 mV or both was greater in patients who eventually had cardiac events, although there were false-positive responses. Complex ventricular arrhythmias occurred in 8 patients, 5 of whom had cardiac events. Seven patients had both ST-segment changes and chest pain with exercise; all had cardiac events, 4 of which were major. Of the 34 patients with deep ST depression (≥0.1 mV), 25 had cardiac events, 14 of which were major, and 1 died.

Rest and exercise radionuclide ventriculography: LV ejection fraction, end-diastolic volume index (EDVI), end-systolic volume index (ESVI), normalized wall motion score and P/V index at rest and the percent change with exercise were determined. These and the peak submaximal exercise values for LV ejection fraction, ESVI, and P/V index are shown in Table IV. The LV ejection fraction, ESVI, and P/V index at rest and submaximal divided according to infarct distribution are shown in Figure 1. Patients with limited nontransmural infarcts had a significantly higher resting LV ejection fraction and P/V index and smaller ESVI than the other groups. During submaximal exercise, they tended to respond normally as a group. The anterior transmural infarct group had the most reduced LV function at rest and as a group had an abnormal response in each of these variables.

Predictive ability of scintigraphic parameters: Patients with cardiac events were compared with those without cardiac events to determine whether any of these variables identifies patients at risk for future ischemic events. Generally, the change with submaximal exercise in LV ejection fraction, ESVI, wall motion score and P/V index were significantly different in patients who had cardiac events compared with those who did not have them, irrespective of infarct distribution (Table IV, Fig. 2). Except for resting LV ejection fraction in the inferior transmural group, wall motion score in the limited nontransmural group and P/V index in the anterior transmural group, the resting LV ejection fractions, ESVIs, wall motion scores and P/V indexes were significantly different in the no-event and cardiac event groups ($p < 0.05$).

Patients without follow-up cardiac events had normal resting LV ejection fractions, EDVIs and ESVIs. They had only mild to moderate resting segmental wall motion abnormalities and reductions in P/V index. These patients tended to respond normally to submaximal exercise with an increase in LV ejection fraction, wall motion score and P/V index and a decrease in ESVI. A small increase in EDVI was found consistently in all infarct groups, independent of follow-up cardiac events.

Comparison of scintigraphic measurements: major versus minor events: The mean rest and peak LV submaximal exercise ejection fractions, ESVIs and P/V indexes for all patient groups according to the specific cardiac events that occurred during follow-up are shown in Figure 3. The peak submaximal exercise LV ejection fractions in the inferior transmural group

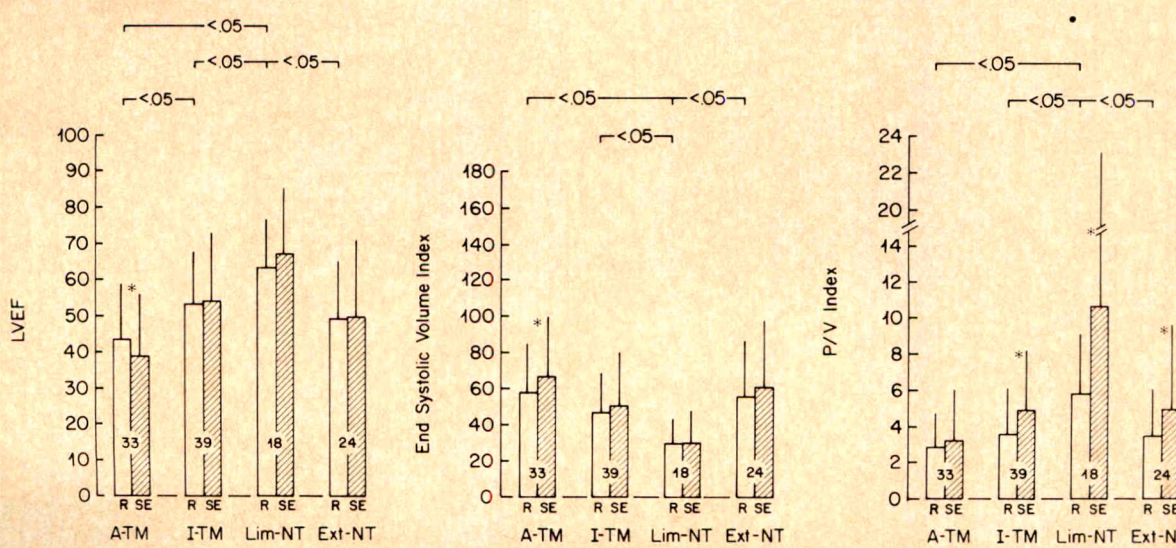

FIGURE 1. Left ventricular ejection fraction (LVEF), end-systolic volume index and pressure/volume (P/V) index at rest (R) and peak submaximal exercise (SE) in patients with anterior transmural (A-TM), inferior transmural (I-TM), limited nontransmural (Lim-NT) and extensive nontransmural (Ext-NT) infarctions. *$p < 0.05$ rest versus submaximal exercise.

TABLE IV Correlates of Rest and Exercise Scintigraphic Variables Versus Cardiac Events

	All Patients			Anterior TM		
	No Event	Minor Event	Major Event	No Event	Minor Event	Major Event
n	43	33	41	6	12	14
LVEF	60.3 ±13.0	47.7 ±16.0	43.7 ±15.3	55.0 ±10.9	42.4 ±15.6	40.1 ±16.1
% units change with exercise	9.1 ±6.1	−6.0 ±7.2	−5.3 ±7.0	6.8 ±10.5	−6.0 ±9.5	−7.2 ±6.0
Peak exercise LVEF	69.4 ±13.3	41.6 ±13.6	38.4 ±18.4	61.8 ±16.2	36.4 ±11.3	32.9 ±14.7
Wall motion score	91.3 ±11.4	75.9 ±15.2	73.8 ±16.1	81.7 ±16.4	68.7 ±15.9	66.2 ±14.1
% change with exercise	1.6 ±5.9	−9.7 ±9.0	−10.6 ±10.4	1.0 ±6.1	−12.3 ±9.3	−6.9 ±5.7
EDVI	84.8 ±26.7	106.9 ±33.9	92.5 ±33.7	88.7 ±10.2	95.2 ±30.0	91.6 ±31.0
% change with exercise	7.0 ±11.4	11.6 ±11.3	11.2 ±11.7	6.4 ±10.8	7.2 ±7.1	13.8 ±15.7
ESVI	37.6 ±20.9	59.3 ±27.6	56.0 ±28.9	42.5 ±13.0	58.9 ±27.4	57.9 ±25.5
% change with exercise	−18.3 ±19.8	25.3 ±21.2	19.1 ±21.0	−9.1 ±28.8	19.6 ±20.2	25.3 ±20.7
Peak exercise ESVI	31.3 ±20.2	71.5 ±31.0	67.7 ±38.5	39.3 ±17.6	67.3 ±27.4	73.0 ±36.0
P/V index	4.7 ±3.0	3.0 ±2.2	3.2 ±2.2	3.3 ±1.2	2.9 ±1.8	2.9 ±2.0
% change with exercise	76.1 ±52.8	5.8 ±28.3	6.2 ±31.0	67.5 ±57.4	6.6 ±41.0	−3.2 ±25.1
Peak exercise P/V index	8.8 ±8.7	3.0 ±1.9	3.5 ±3.0	5.4 ±2.8	3.0 ±1.8	2.8 ±2.4

EDVI = left ventricular end-diastolic volume index; ESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction NT = nontransmural; P/V index = systolic blood pressure/left ventricular end-systolic volume index; TM = transmural.

was significant in distinguishing major and minor cardiac events ($p < 0.05$). Otherwise, there were no consistent differences between major and minor event groups for these variables. The patients with limiting angina had the least abnormal and those patients that died and had persistent congestive heart failure the most abnormal findings (Fig. 3). In response to submaximal exercise, all the event groups had a similar response, and one essentially opposite to that in patients without cardiac events.

Predictive ability of clinical, submaximal exercise test and scintigraphic variables: A stepwise multivariate discriminant function analysis was conducted to test the ability of the clinical, exercise and

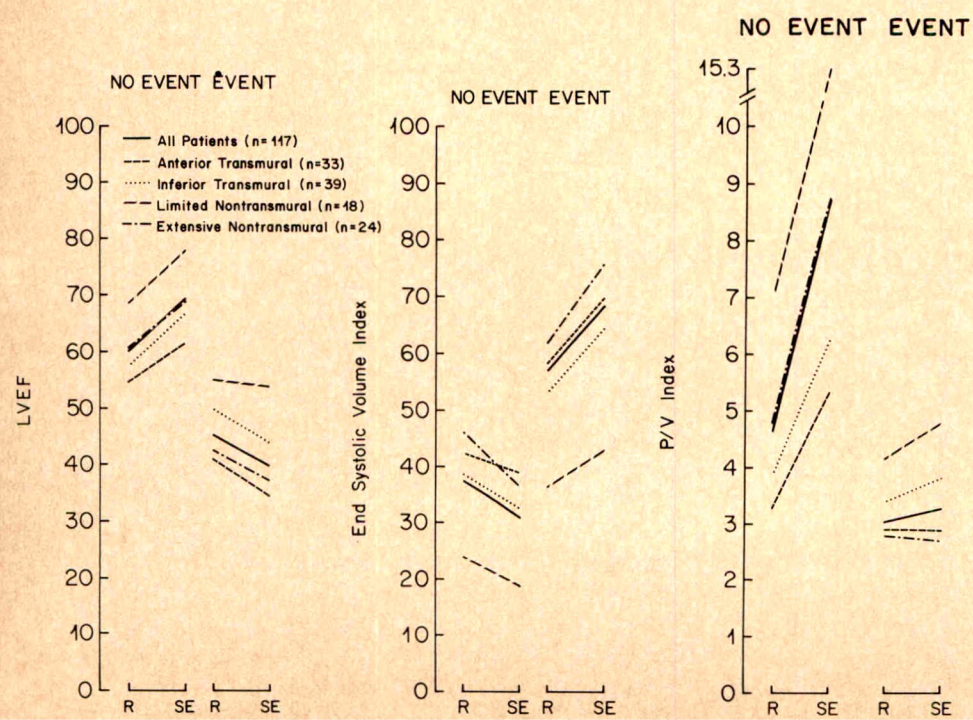

FIGURE 2. Left ventricular ejection fraction (LVEF), end-systolic volume index and pressure/volume (P/V) index at rest (R) and peak submaximal exercise (SE) in patients with and without cardiac events.

TABLE IV, continued

Inferior TM			Limited NT			Extensive NT		
No Event	Minor Event	Major Event	No Event	Minor Event	Major Event	No Event	Minor Event	Major Event
18	10	12	10	3	5	9	8	7
57.6 ±10.9	58.1 ±14.9	44.3 ±15.7	69.9 ±11.9	51.7 ±12.6	58.2 ±9.3	58.5 ±15.6	43.4 ±16.1	44.4 ±12.0
9.3 ±5.5	−7.3 ±6.9	−5.2 ±8.8	8.3 ±3.1	−4.0 ±2.0	−0.4 ±10.9	11.3 ±6.3	−6.0 ±5.3	−6.7 ±8.0
66.9 ±9.7	50.8 ±14.5	39.1 ±20.9	78.2 ±11.7	47.7 ±11.9	57.8 ±17.3	69.8 ±16.0	37.4 ±13.2	37.7 ±17.0
92.2 ±8.9	84.4 ±13.9	73.9 ±16.7	95.0 ±11.7	88.3 ±11.9	95.0 ±17.3	91.7 ±13.8	73.8 ±11.3	77.1 ±10.6
1.8 ±6.7	−6.9 ±8.3	−11.0 ±12.8	0.0 ±4.6	−6.7 ±14.1	−9.4 ±11.0	0.0 ±5.6	−10.7 ±8.2	−17.0 ±12.2
85.5 ±21.6	119.3 ±37.4	87.8 ±20.9	71.6 ±19.2	80.0 ±9.8	74.4 ±16.6	95.7 ±43.6	117.3 ±36.9	91.9 ±36.5
7.0 ±14.4	11.8 ±11.7	7.3 ±7.0	7.3 ±9.0	24.2 ±24.1	8.3 ±8.0	7.2 ±8.8	13.4 ±8.9	15.1 ±12.3
39.0 ±13.2	55.8 ±32.2	51.8 ±21.2	24.3 ±10.4	40.7 ±14.6	34.2 ±13.3	46.1 ±36.9	68.0 ±27.1	54.6 ±27.2
−14.6 ±18.0	31.4 ±25.6	14.4 ±20.5	−27.1 ±19.2	33.1 ±30.3	8.1 ±25.1	−22.0 ±15.4	25.8 ±15.7	24.5 ±20.9
32.9 ±13.3	70.9 ±42.8	60.3 ±27.0	19.1 ±11.3	52.3 ±15.4	37.8 ±20.2	36.6 ±33.9	83.1 ±25.7	68.7 ±40.4
3.9 ±2.2	3.6 ±3.4	3.2 ±2.3	7.1 ±3.7	3.9 ±1.5	4.3 ±2.0	4.8 ±2.9	2.2 ±0.9	3.5 ±2.8
72.6 ±40.7	5.1 ±24.3	14.6 ±35.6	86.5 ±75.7	6.3 ±7.4	24.8 ±43.4	77.6 ±49.1	6.4 ±17.5	−0.1 ±21.5
6.3 ±2.5	3.4 ±2.6	4.1 ±4.2	15.3 ±15.6	4.1 ±1.6	5.2 ±2.3	8.8 ±5.7	2.2 ±0.9	3.3 ±2.3

scintigraphic variables to predict future cardiac events (Table V). Table VI summarizes the results of this analysis and lists the "jack-knifed" percentage of patients classified correctly for all patients and the patients grouped according to infarct distribution.

Prediction: cardiac event versus no cardiac event: The change in ejection fraction with submaximal exercise was rated the most important variable in the first step of the discriminant analysis and classified correctly 89% of the 117 patients into event and no event groups. The ΔESVI with submaximal exercise was ranked a close second in the initial step of the discriminant analysis of all patients and was entered first in the analysis of limited and extensive nontransmural infarcts (Table VII), correctly classifying 84 and 96% of patients, respectively. As for the entire group, the ΔLV ejection fraction entered first in the inferior transmural infarcts and classified correctly 87%. In patients with anterior transmural MI, the LV ejection fraction at peak submaximal exercise entered first and classified 84% of the patients correctly.

Prediction: major cardiac event versus minor cardiac event: The discriminant function entered the same variables (ΔLV ejection fraction, ΔESVI and peak LV ejection fraction) in the initial step when separating patients into major and minor events and no-event groups. When this additional requirement was made, the ΔLV ejection fraction correctly classified only 61% in the first step. By the addition of LV ejection fraction at peak submaximal exercise, ST depression of ≥0.1 mV, the ΔESVI, work load completed during submaximal exercise and ΔEDVI, 74% were classified correctly. The analysis of the individual infarct groups showed 50 to 63% correctly classified in the initial step. The reduced discriminating power was primarily one of clas-

TABLE V Clinical, Exercise, and Radionuclide Ventriculographic Variables Used in Discriminant Analysis

Clinical	Submaximal Bicycle Exercise	RVG*
Age	Maximum work load	LVEF
Sex	Angina pectoris	Wall motion score
History of previous MI	ST alteration†	End-diastolic volume
Infarct location	Ventricular ectopy	. . .
Killip class	Change in heart rate	End-systolic volume
	Change in blood pressure	P/V index

* Both rest and exercise values were used in addition to the change to peak exercise.
† ST depression (0.05 mV) or elevation (0.1 mV).
LVEF = left ventricular ejection fraction; MI = myocardial infarction; P/V index = systolic blood pressure/left ventricular end-systolic volume index; RVG = radionuclide ventriculogram; ST = ST segment.

TABLE VI Results of Multivariate, Discriminant-Function Analysis According to Degree of Left Ventricular Dysfunction

	LVEF <40% (n = 29)		LVEF ≥40% (n = 88)	
No event versus any event	1. Peak LVEF	90%	1. ΔLVEF	89
	2. ΔESVI	97%	2. Peak LVEF	93
	3. Killip class	100%	. . .	

ESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SE = submaximal exercise.

TABLE VII Results of Multivariate, Discriminant-Function Analysis of All Clinical, Exercise and Scintigraphic Variables at 6-Month Follow-Up

	All Patients (n = 117)	Anterior TM (n = 33)	Inferior TM (n = 39)	Limited NT (n = 18)	Extensive NT (n = 24)
No event versus any event	1. ΔLVEF 89%	1. Peak LVEF 84%	1. ΔLVEF 87%	1. ΔESVI 84%	1. ΔESVI 96%
	2. Peak LVEF 91%	2. Age 90%	2. WMS 90%	2. SE pain 89%	2. ΔWMS 96%
		3. ΔLVEF 94%		3. ST changes 89%	3. SE pain 100%
				4. ST ↓ 0.1 mV 94%	
				5. ΔBP 94%	
				6. ΔWMS 100%	

BP = systolic blood pressure; ESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; NT = nontransmural; SE = submaximal exercise; ST = ST segment; TM = transmural; WMS = wall motion score; Δ = change with exercise; ↓ = depression.

sifying patients into the wrong event group, i.e., 10 of 33 with minor events were classified as major and, conversely, 12 of 41 with major events were classified as minor. Only 3 of 43 patients without cardiac events and 6 of 74 with cardiac events were misclassified.

Predictive ability according to degree of resting left ventricular dysfunction: The patients with anterior transmural MI had the most severe LV dysfunction with exercise (Fig. 1). Furthermore, the discriminant function entered the LV ejection fraction at peak submaximal exercise in the first step, unlike the other groups in which the ΔLV ejection fraction or ΔESVI entered first. Because of this, separate analysis of those patients with LV ejection fractions <0.40 and ≥0.40 were performed (Table VII). The LV ejection fraction at peak submaximal exercise entered first in the group with resting LV ejection fractions <0.40 and correctly classified 90% of patients into event and no event groups and 66% into major, minor and no-event groups. The analysis of those patients with LV ejection fractions ≥ 40% provided the same information as that described for the entire group of 117 patients (Table VI). It should be noted that 26 of 29 patients with LV ejection fractions <0.40 had cardiac events, whereas 48 of 88 patients with LV ejection fractions ≥0.40 had cardiac events (p <0.001).

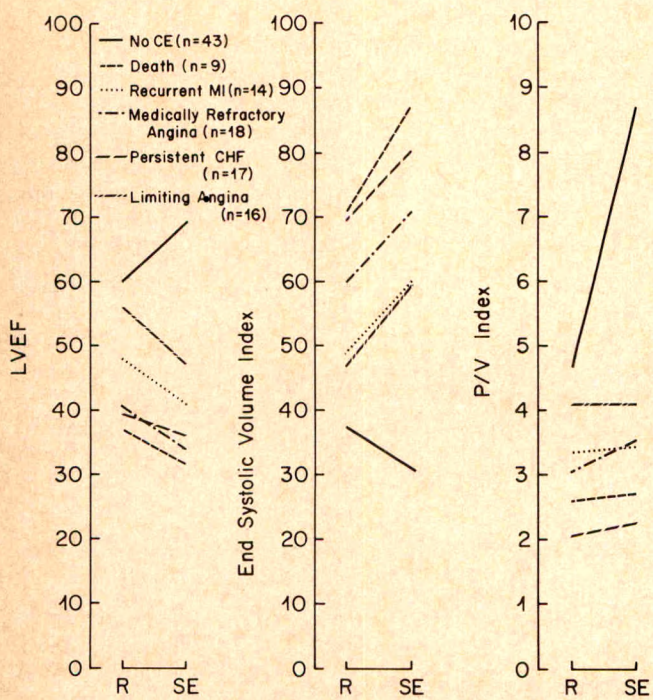

FIGURE 3. Left ventricular ejection fraction (LVEF), end-systolic volume index and pressure/volume (P/V) index at rest (R) and peak submaximal exercise (SE) according to specific cardiac events (CE) during follow-up. CHF = congestive heart failure; MI = myocardial infarction.

Sensitivity and specificity of predictive variables: The sensitivity, specificity and predictive accuracy for the scintigraphic variables, the exercise electrocardiogram, and a history of MI are shown in Table VIII. Overall, the change in LV ejection fraction, ESVI and P/V index were accurate in predicting prognosis, particularly at 6-month follow-up, by which time 9 additional patients had had cardiac events and had changed from having false- to true-positive results. The change in wall motion score was the next best indicator, with a sensitivity, specificity, and predictive accuracy of 79% at 6 months. The change in LV ejection fraction, ESVI, and P/V index were all significantly better in classifying patients than ST-segment changes during submaximal exercise, an LV ejection fraction <0.40 at rest and a history of MI (p <0.001). They were also better than changes in wall motion score (p <0.005). These same general relations were maintained even when the patients were grouped according to infarct distribution (Table VIII). In those patients who had no cardiac event after 6 months of follow-up, 37 of 43 (86%) had a normal response of both LV ejection fraction and ESVI to submaximal exercise, and 35 of these 37 patients had a normal P/V index response as well.

Discussion

This study demonstrates that submaximal exercise with RVG can be performed safely 2 to 3 weeks after MI, and that it is effective in identifying patients most and least likely to have cardiac events in the ensuing 6 months. These findings support our observations in 61 patients[18] and demonstrate that patients can be separated into 2 groups: 1 with a low probability of further cardiac events and 1 with a high probability of cardiac events. This prognostic separation of patients can be made irrespective of MI location and type.

After 6 months, 74 of the 117 study patients had cardiac events: 41 died or had a recurrent MI or medically refractory angina and 33 patients had persistent congestive heart failure or limiting angina. Between 3 and 6 months of follow-up, 2 patients who had not had cardiac events at 3-month follow-up and 13 patients who had minor cardiac events progressed to at least 1 major event. Each had abnormal scintigraphic evaluations initially.

Patients in this study continued receiving medical therapy during exercise testing and after discharge. Furthermore, an abnormal result was related to the responsible physician so that an effort could be made to optimize their management. This differs from most other studies of a similar patient population and may account for the relatively low incidence of death (8%) in our patients.[21,22,41]

Like many other centers performing equilibrium exercise RVG, our patients were exercised supine with a bicycle ergometer.[41,42] This differs from most other studies of this type, which are performed upright with a treadmill or bicycle ergometer.[21–25,27] Also, the Frank (X,Y,Z) lead system was used to monitor patients during exercise.[32] Blackburn[33] showed that the ST-segment vector of Frank leads are approximately half that of standard leads or a bipolar V_5.[33] When this information is taken into account, however, the sensitivities of the 2 systems are reported to be comparable.[34] Regardless, this may have contributed to the relatively poor sensitivity and specificity of the exercise electrocardiogram in this study.

Our patients were separated into groups according to MI distribution. As would be expected, patients with anterior transmural MI had a higher incidence of cardiac events ($p = 0.01$) than the other groups. They also may have had an increased incidence of diabetes mellitus ($p = 0.063$) and, as others have shown, the poorest LV function at rest and during exercise (Fig. 1).[4,5,8,10,26] The frequency of previous MI may have been increased in the extensive nontransmural group ($p = 0.055$). The limited nontransmural group was similar to the patients evaluated by Lown,[43] Rigo,[44] Mahoney,[45] and coworkers who had normal QRS complexes, that is, only ST and T-wave changes on the electrocardiogram and a "mild course" after discharge. Four patients in this group did have a previous MI and 2 had abnormal QRS complexes. One patient had lost previously significant Q waves in the inferior leads and 1 had a previous nontransmural MI. Although this group clearly had the best resting LV ejection fractions (Fig. 1), 8 of 18 had follow-up cardiac events, 5 of which were major. Three of the 4 patients with previous MIs, none of whom had resting LV ejection fractions of <0.40, had cardiac events. However, even if they were eliminated from the group, the incidence of cardiac events was not different from that in patients with inferior transmural and extensive nontransmural MIs. The extensive nontransmural group had significantly larger LV volumes and poorer LV function, similar to the patients in Rigo's "nontransmural-B" category.[44] Nevertheless, their prognosis was no worse than that for patients with limited nontransmural MIs.

TABLE VIII Sensitivity, Specificity, and Predictive Accuracy of Radionuclide Ventriculographic, Electrocardiographic, and Clinical Variables for Predicting Follow-Up Cardiac Events at 6 Months Follow-Up: All Patients and Individual Infarct Groups

	All Patients (n = 114)			Anterior TM (n = 33)			Inferior TM (n = 39)			Limited NT (n = 18)			Extensive NT (n = 24)		
	Sen	Spec	Acc	Sen	Spec	Acc	Sen	Spec	Acc	Sen	Spec	Acc	Sen	Spec	Acc
Failure of LVEF to increase with submaximal exercise	94	91	93	93	67	88	95	89	92	88	100	94	100	100	100
Increase in ESVI with submaximal exercise	90	93	91	93	83	91	86	95	90	88	100	94	93	89	92
Failure of P/V index to increase ≥35% with submaximal exercise	93	86	90	89	67	85	95	89	92	88	90	89	100	89	96
Decrease in wall motion score	79	79	79	81	83	82	76	72	74	63	89	72	87	89	88
LVEF <40%	35	93	56	44	83	52	38	95	67	0	100	56	40	89	58
Exercise ST↓ (0.05 mV)	63	56	61	67	33	60	67	50	59	63	90	78	67	33	54
Previous MI	35	86	54	26	67	33	50	94	61	37	90	67	67	78	71

Acc = predictive accuracy; ESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT = nontransmural; P/V index = systolic blood pressure/left ventricular end-systolic volume index; Sen = sensitivity; Spec = specificity; ST↓ = ST-segment depression.

Only Pulido,[26] Borer,[41] Corbett,[18] and their coworkers have reported evaluations of the usefulness of submaximal exercise and RVG in patients after MI. Borer et al found little difference in resting ventricular function between the different MI groups even when patients with first MIs were compared. Further, he found little variation in LV ejection fraction with submaximal exercise and felt that it was of no additional help in identifying patients who died, all of whom had resting LV ejection fractions <0.35. We found, as did Pulido et al, significant differences in resting LV function with different MI distributions (Fig. 1) even when patients are separated according to the presence or absence of follow-up cardiac events (Fig. 2). The patients with follow-up cardiac events in this study had significantly lower resting LV ejection fractions and P/V indexes and larger LV volumes. Although 26 of 29 patients with resting LV ejection fractions <0.40 had cardiac events, 48 of 88 (55%) patients with resting LV ejection fractions ≥0.40 also had cardiac events.

Our data emphasize that the change in LV ejection fraction and end-systolic volume index with submaximal exercise are the best predictors of cardiac events during the subsequent 6 month follow-up.[18] Except for patients with anterior transmural MIs, these scintigraphic parameters were entered first by the stepwise multivariate discriminant analysis (Table VI), and were consistently ranked first and second in the initial step. They had the best sensitivities, specificities and predictive accuracies independent of MI distribution (Table VIII). The LV P/V index was consistently the third highest rated variable in the first step of the discriminant analysis. Most of the patients in the present study had significant changes in LV function with exercise. Thirty-nine of 41 patients without cardiac events had an increase in LV ejection fraction of ≥0.05 and 56 of 74 patients with cardiac events had a decrease in LV ejection fraction with submaximal exercise, 44 by >0.05. The discriminant function was less successful in classifying patients into "no cardiac event," "minor cardiac event" and "major cardiac event" groups than simply into event and no-event groups. This is similar to the findings in our preliminary report in fewer patients.[18]

The patients with anterior transmural MI were found by the discriminant function to have their prognosis predicted best by the peak submaximal exercise LV ejection fraction (Table VII). This was also the case when only patients with LV ejection fractions <0.40 were analyzed. However, these 2 groups were not entirely comparable; only 13 of 33 patients with anterior transmural MIs had resting LV ejection fractions <0.40. Despite these differences, the peak submaximal exercise LV ejection fractions appeared to provide the most prognostic information in the patients with the most severe LV dysfunction.

Most previous studies of prognosis after MI were performed before the general availability of scintigraphic techniques for the evaluation of ischemic heart disease.[3,4,22,43] Because of this, previous exercise studies have relied almost exclusively on the electrocardiogram and other noninvasive hemodynamic measurements.[21–25] We also found electrocardiographic S segment depression to be predictive of cardiac even (Table III). However, the predictive accuracy of th variable was only 61%, significantly less than the chan with submaximal exercise in LV ejection fractio end-systolic volume index and the LV P/V index <0.001). Recently, submaximal exercise and thalliur 201 scintigraphy were used in 2 studies to detect th presence of multivessel coronary artery disease after M and predicted 83 and 63%, respectively, of stenose vessels supplying myocardium at risk.[46,47] Neither these studies specifically addressed follow-up prognosi Silverman et al[17] used a quantitative assessment thallium-201 defect size to predict longer-term pro nosis. A large defect was predictive of follow-up mo tality.[17]

In summary, this study confirms that submaxim exercise RVG performed before hospital discharge aft MI is usually safe, convenient, and helpful in the ide tification of those patients at risk for further cardi events. This capability exists independently of MI l cation and the degree of LV dysfunction at rest ar applies to patients with either transmural and no transmural MI.

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Intracoronary Thrombolysis in Acute Myocardial Infarction

WILLIAM GANZ, MD

Forty-seven patients with acute myocardial infarction (MI) underwent intracoronary infusion of Thrombolysin® or streptokinase. In 41, a completely reoccluded artery was reopened. Patency was associated with appearance of arrhythmias, relief of pain, gradual return of the ST-segment to the baseline and appearance of abnormal Q waves. Creatine kinase (CK) and MB-CK enzyme levels peaked earlier. Serial thallium scintigrams showed reduction in defect size after reperfusion, and the ejection fraction was higher compared with control. Eighteen patients were recommended for coronary bypass surgery for recurrent pain or severe multivessel disease.

Massive necrosis remains the principal cause of death and morbidity among patients hospitalized with acute myocardial infarction (MI). Extensive infarcts induce heart failure, cardiogenic shock and malignant dysrhythmias. Interventions designed to minimize myocardial necrosis by reduction of myocardial oxygen demand, augmentation of collateral blood supply and correction of various ischemic cellular defects have not been sufficiently effective in patients with MI. It is becoming increasingly apparent that anterograde flow to the ischemic myocardium must be restored to salvage substantial quantities of jeopardized myocardium and to improve the prognosis of patients with MI.

Coronary Artery Reperfusion

Physiologic background: In dogs, myocardial necrosis may begin as early as 20 minutes after coronary artery occlusion and then progress in a wave front from the subendocardium toward the epicardium. The rate and extent of necrosis varies depending on the site of occlusion, the presence of collateral channels and on hemodynamic and metabolic variables that affect collateral blood flow and myocardial oxygen demand. In some dogs, transmural necrosis was observed after only 40 minutes of coronary artery occlusion; in others, little necrosis was present after 3 to 6 hours of occlusion. In most dogs and monkeys, the process of necrosis is practically complete after 6 hours of coronary artery occlusion.[1,2] The rate of necrosis in humans is affected by additional factors, such as the rate and completeness of coronary occlusion and the presence and extent of acquired collaterals. In patients with acute MI at highest risk, the ischemia is extensive and severe.[3] In such patients, the time limit for clinically meaningful reperfusion is probably substantially less than 6 hours. On the other hand, in patients with extensive collaterals or incomplete occlusion of the coronary artery, significant myocardial salvage is probably possible well beyond 6 hours.

Markers of reversible injury: Because of a wide variation in the time course of necrosis, the availability of markers of reversible or irreversible injury would be of great value for assessing the likelihood of significant myocardial salvage in a given patient.

The electrocardiogram: Isolated T-wave abnormalities suggest reversible myocardial ischemia, whereas ST deviations are consistent with both reversible and irreversible injury. Abnormal Q waves usually indicate myocardial necrosis. Experimental studies as well as clinical experience in patients with successful intracoronary thrombolysis, however, indicate that the development of electrocardiographic signs of necrosis often lags several hours behind the anatomic course of necrosis. Thus, the absence of Q waves and R-wave diminution in the first hours of an acute MI does not rule out that the injury is already irreversible.

Myocardial enzymes: Abnormally elevated activity of serum creatine kinase (CK) and other myocardial enzymes are, in general, considered indicative of myocardial necrosis. The enzyme molecules released from the irreversibly injured myocardial cells initially remain in the myocardium and are only slowly carried into the systemic circulation by the collateral blood circulation and the lymphatic vessels. It is not surprising, therefore, that animal studies as well as clinical experience in patients who underwent successful intracoronary thrombolysis indicate a significant time lag between the course of anatomic necrosis and the abnormal elevation of enzyme activity in the serum, since normal serum levels of myocardial enzymes in the first hours of an acute MI do not rule out the presence of extensive necrosis.

Regional wall motion abnormalities: The myocardium becomes dyskinetic seconds after occlusion of a coronary artery. Regional wall motion abnormalities

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are not helpful in differentiating reversible ischemia from irreversible injury in the early hours of an acute MI.

Coronary thrombosis: Numerous studies in recent years have confirmed that thrombosis is usually the mechanism of coronary artery occlusion in transmural MI. The frequency of thrombotic occlusion in autopsy studies ranged from 88 to 97.5%.[4] In vivo angiography and retrieval of thrombi by the surgeon in most patients with acute MI undergoing coronary bypass operation support the postmortem findings. Thrombosis in the coronary artery is triggered by rupture of an atherosclerotic plaque.[5] Experience in patients with acute MI undergoing nonsurgical reperfusion indicates that spasm, contrary to previous reports, is rarely, if ever, the cause of coronary artery occlusion.

Coronary thrombolysis in acute myocardial infarction: Multicenter trials were conducted to determine whether lysis of the coronary artery thrombus would reduce mortality in patients with acute MI. These studies used intravenous streptokinase or urokinase.[6] The initial trials indicated a reduction in mortality; later studies conducted under more rigorously controlled conditions failed to confirm the early findings. A recent study conducted in Europe[7] reported a reduction in mortality. The main weakness of these studies was that treatment was begun too late to seriously reduce myocardial damage. Experimental evidence suggests that systemic thrombolysis is slow and unreliable. Clinical studies are being conducted in which streptokinase is administered early and its effect on coronary patency is assessed by angiography. These studies should determine the role of systemic thrombolysis in the management of acute MI.

Intracoronary thrombolysis: Experimental studies in our laboratory and elsewhere demonstrated that intracoronary thrombi can be lysed rapidly (within minutes) by local application of thrombolytic agents. In vivo and in vitro studies using a mixture of streptokinase and plasminogen (Thrombolysin®) also showed that the rapidity of thrombolysis increases with the concentration of the thrombolytic agent at the clot. Histologic study of the coronary artery and the myocardium exposed to several hours of Thrombolysin infusion revealed no toxic effects attributable to the infusion.

Relevance of intramyocardial bleeding after coronary reperfusion: It was suggested previously[8] that reperfusion of an occluded coronary artery might be detrimental in that it could produce intramyocardial hemorrhage. However, labeling of microvascular damage with colloidal carbon proved that intramyocardial hemorrhage after reperfusion is the consequence of ischemic microvascular injury present before reperfusion and found in areas of most advanced myocardial necrosis, predominantly in the subendocardium.[8]

Mechanical function after reperfusion: The mechanical function of the reperfused myocardial region usually remains markedly depressed. Although during coronary occlusion the ischemic myocardium cannot increase its contractile function in response to inotropic stimulation, after reperfusion the depressed mechanical function of the previously ischemic myocardium can be substantially improved by inotropic stimulation. These findings suggest that intractable heart failure caused by extensive myocardial ischemia and unresponsive to inotropic stimulation could be successfully treated by early reperfusion and inotropic enhancement.

Clinical studies: Patients with evolving myocardial infarction likely to benefit from reperfusion of the occluded coronary artery are candidates for intracoronary thrombolysis. The following criteria are used for patient selection. The patient is seen within 3 hours of the onset of chest pain; the pain is not relieved by nitroglycerin; the electrocardiogram manifests ST-segment elevation ≥3 mm with reciprocal ST depression; there is no contraindication to anticoagulation; the patient consents to the procedure or the patient's relatives and the patient's primary physician consent to it.

In the catheterization laboratory, an indwelling Longdwell Teflon™ needle is placed in the left femoral artery for arterial pressure, monitoring, and blood sampling. An 8F Judkins angiography catheter is inserted into the right femoral artery. A 2,500-IU bolus of heparin is administered intravenously. In patients with anteroseptal infarction, the right coronary artery is visualized in a single view. In patients with inferior infarction, the left coronary artery is visualized first, because the right coronary artery is more likely to be the site of occlusion. Nitroglycerin, 0.1 mg in 2 ml of 5% dextrose, is injected slowly into the occluded coronary to rule out that the occlusion is caused by spasm. Heparin, 5,000 IU, is added intravenously.

For infusion of the thrombolytic agent, a special radiopaque catheter (coronary infusion catheter, American Edwards Laboratories) 2.5F in diameter is inserted through the lumen of the angiography catheter. The distal 20-cm segment of the catheter is reduced to a 2F diameter, and is very soft and flexible to prevent mechanical damage to the coronary artery. To facilitate precise location, the tip is made strongly radiopaque so that it can be seen inside the angiographic catheter. The infusion catheter is advanced to the site of occlusion. The propriety of catheter position is checked in at least 2 views. The infusion catheter is slightly stretched to eliminate redundancy and to prevent the catheter from moving downstream when the artery becomes partially patent. During infusion of the thrombolytic agent, the angiography catheter remains in the ostium of the coronary artery. The space between lumen of the angiographic and the infusion catheter allows continuous monitoring of the intracoronary pressure and intermittent injection of contrast material to check whether the artery is patent, without interrupting the treatment. Streptokinase is injected at a rate of 2,000 IU in 1 ml of saline/min, until arterial patency is achieved, but no longer than 100 minutes. When the artery is reopened, the infusion is reduced to 1,000 IU/min and maintained for an additional 60 minutes. The protracted infusion is necessary because at the time of initial patency the clot is usually not completely lysed; discontinuation of thrombolysis at that point could result in regrowth of the thrombus and reocclusion.

After termination of the thrombolysis, coronary angiography is completed and left ventriculography is

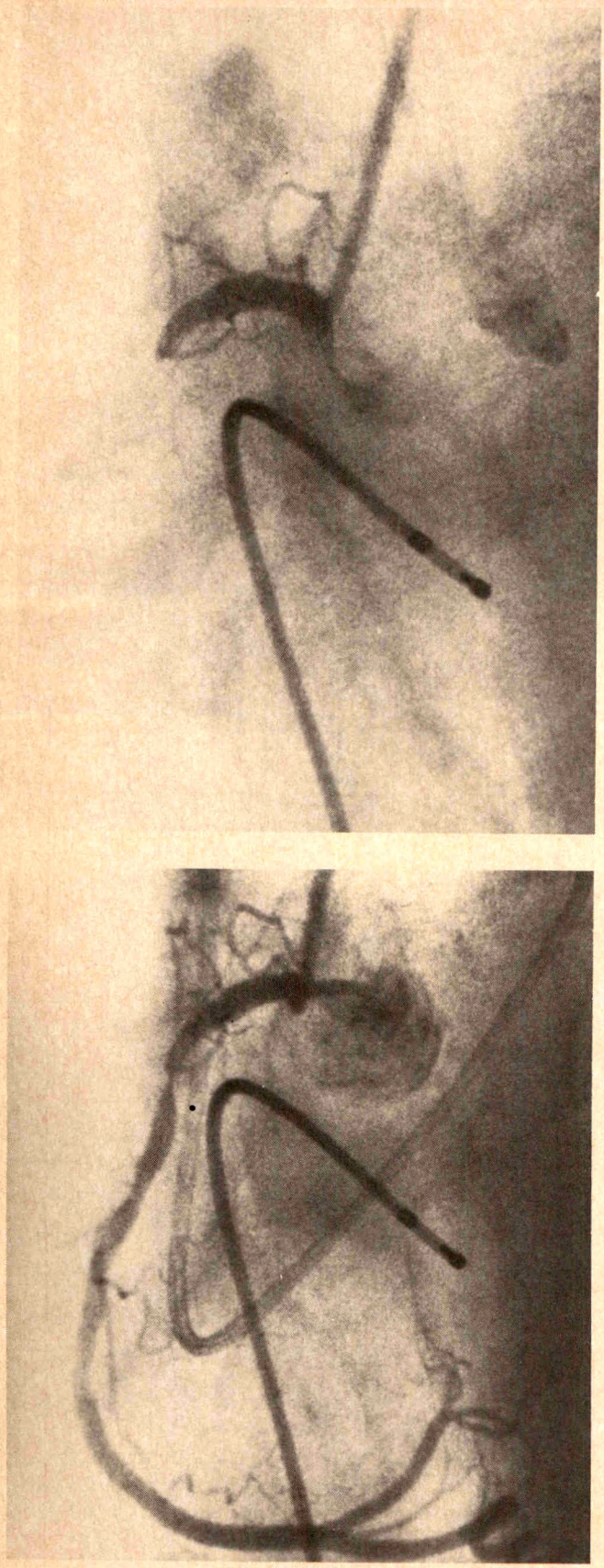

FIGURE 1. Angiograms of the right coronary artery in a patient admitted after 1 hour of chest pain with electrocardiographic signs of an acute inferoposterolateral infarction. **Top,** Before intracoronary thrombolysis. **Bottom,** At the completion of the procedure. The patient received a total of 300,000 IU of Thrombolysin® in 75 minutes.

performed. After the procedure, the patient is tran ferred to the cardiac intensive care unit. When th partial thromboplastin time returns to below twi control, the angiography catheter is removed from th groin. After hemostasis, an infusion of heparin is in mediately begun at a rate of 800 to 1,000 IU/h to mai tain partial thromboplastin time between 1.5 and times control. After several days, warfarin is substitute for heparin and maintained for 3 months. Anticoag lation is limited to 3 months on the assumption tha thrombosis of the coronary artery was triggered by defect in the endothelium secondary to rupture of th plaque, and that the defect will be healed and becom nonthrombogenic during this period.

Intracoronary infusion of Thrombolysin or strep tokinase resulted in reopening of the completely oc cluded artery in 41 to 47 patients (Fig. 1). The lumen a the completion of Thrombolysin infusion was usuall larger than at the time of initial patency, suggestin further lysis of the clot. In 3 of 5 patients who wer restudied 10 to 14 days after thrombolysis, the lume size further increased, suggesting either further lysis c the clot or shrinkage of the underlying atherosclerot plaque; in 2 patients there was no appreciable chang in lumen size.

Patency was frequently signaled by the appearanc of ventricular dysrhythmias like premature ventricula complexes, bigeminy or isorhythmic dissociation. Tw patients had ventricular tachycardia and 1 ventricula fibrillation; all 3 responded to electrical conversion Patency was followed by relief of pain, gradual retur of the ST segments to the baseline and, frequently, b development of abnormal Q waves, indicating that som necrosis had occurred before reperfusion. Atrioven tricular and intraventricular conduction abnormalitie due to the recent coronary artery occlusion disappeare immediately after reopening of the artery. All of ou patients had normal serum CK and MB-CK levels be fore reperfusion. The enzymes began to increase im mediately after reperfusion and reached a peak 6 to 1 hours earlier than in the absence of reperfusion. Ex perimental studies suggest that the enzyme peak i about twice as high for the same amount of necroti myocardium than in the absence of reperfusion.

In 18 patients, elective surgery was recommende because of severe multiple vessel involvement or re current angina. The operation was generally well tol erated.

Thallium-201 scintigraphy was performed befor thrombolysis after intravenous injection of about 2 mC of the isotope and after intracoronary injection of 25 t 35 μCi of thallium-201 about 1 hour after reopening th artery and 10 days later after a second intravenou dose.[9] The scintigrams demonstrated significant re ductions in defect size after reperfusion in almost al patients, and virtually complete restoration in some. I our control patients with total coronary artery occlusion the defect size showed no change in the late study Studies of global and regional left and right ventricula function using multiple-gated blood pool scintigraph showed significantly higher ejection fractions after re perfusion than in the control group of patients withou

coronary reperfusion. Wall motion and global function showed further improvement 10 to 14 days after reperfusion. Similar results were reported from other centers.[10–14]

Perspectives

Intracoronary thrombolysis appears to be a relatively safe and effective way of reopening the occluded coronary artery in patients with evolving myocardial infarction. The clinical results are promising, notwithstanding that reperfusion is performed relatively late—3 to 5 hours after the onset of infarct symptoms. The results should significantly improve with earlier hospitalization and by administration of drugs that slow necrosis in the period preceding the reperfusion.

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Coronary Artery Surgery in Australia

Report from the Committee of the National Heart Foundation Coronary Artery Surgery Register

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Clinical data on all patients who have undergone coronary artery surgery in Australia are collected, audited, and published each year by the National Heart Foundation of Australia. These data from 1971 to 1980 are summarized and show the indications for operation, the variation in numbers of patien operated on in each state and unit, and the over increase in number of operations during t decade.

Australia is a country of 15 million people spread out over a continent approximately the size of the United States. Most of the population lives in large coastal cities, Sydney and Melbourne. As in many Western nations, coronary artery disease is the leading cause of death and is responsible for much disability and suffering.

Australia has 9 cardiac surgical units with 40 surgeons attached to them. Coronary artery surgery was first performed in 1970 and is now the most frequently performed major surgical procedure in this country.

The National Heart Foundation of Australia is an organization devoted to the education and research aspects in heart disease. As a national body it advises the government and community on cardiac disease. The Foundation has maintained a register of all open heart surgery since it began in Australia in the mid-1950s. Because of the medical, sociologic and economic implications of coronary artery surgery, a register of all patients operated on in Australia was established by the National Heart Foundation. Individual units complete clinical details of patients operated on and forward these to the National Heart Foundation headquarters in Canberra, where the data are processed and entered on computer. An audit is done and a report is published each year regarding all patients who have had coronary artery surgery in Australia.

The register is maintained by the staff of the National Heart Foundation. The results are reviewed by a vol-

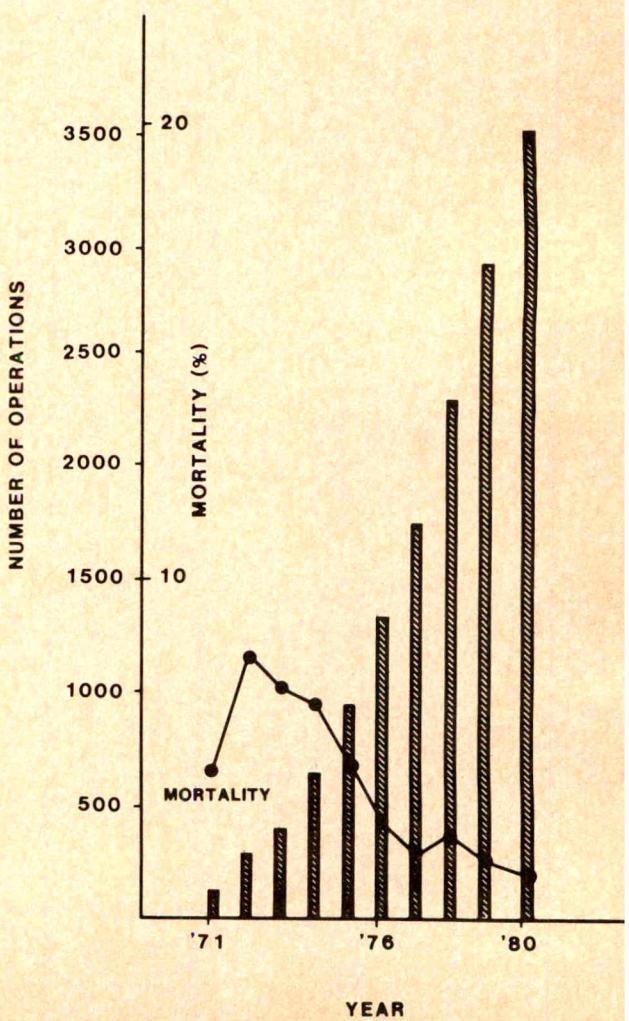

FIGURE 1. Coronary artery bypass graft surgery in Australia.

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TABLE I National Heart Foundation of Australia Coronary Artery Surgery

Year	No. of Cases	Average No. of Grafts per Patient	Mortality (%)
1971	158	1.6	4.4
1972	283	1.8	7.8
1973	366	2.0	7.1
1974	621	1.9	6.4
1975	1,070	2.2	5.2
1976	1,506	2.2	3.2
1977	1,977	2.5	2.9
1978	2,579	2.6	2.3
1979	3,233	2.75	2.0
1980	4,235	2.3	1.79

TABLE II Case Load Per Unit in Australia in 1980

Unit	Cases (n)
1	43
2	347
3	354
4	374
5	428
6	436
7	472
8	506
9	880

TABLE III Variation by State in Number of Operations

State	1974	1980
Queensland	33.1	190
New South Wales	105.4	359
Victoria	51.3	214
South Australia	146.6	675
Western Australia	20.4	283
Rate per million of population		

TABLE IV Indication for Operation (Grafts Only)

Indication	%
Angiographic abnormality only	0.5
Stable angina	73.4
Unstable angina	22.9
Recurrent arrhythmia	0.2
Acute infarction	0.8
Reoperation	1.5

TABLE V Hospital Variability in the Stable/Unstable Angina Ratio

Hospital	Range	Ratio
1	5.1–8.4	6.9
2	0.5–0.9	0.7
3	11.9–35.4	20.5
4	21.8–26.0	23.9
5	0.9–3.0	1.8
6	1.9–4.4	3.0
7	26.4–45.3	33.1
8	1.24–1.5	1.37
9	1.0–1.5	1.4

TABLE VI Relation of Mortality to Extent of Disease (Grafts Only)

	Incidence (%)	Mortality (%)
1-vessel disease	7.3	0.4
2-vessel disease	18.2	0.9
3-vessel disease	56.6	1.6
Left main disease	17.7	2.5

TABLE VII Number of Grafts Placed Per Patient

	Cases (n)	Mortality (%)
1	303	0.7
2	754	1.0
3	1,318	1.7
4	960	1.56
5	325	2.46
6	86	0.1
7	11	0
8	2	0

TABLE VIII Influence of Age and Sex on Operative Mortality Rate (%)

	Age (yr)		
	<50	50–59	60+
Grafts only			
Males	0.5	0.7	2.0
Females	0	2.8	2.5
Grafts plus			
Males	0.9	2.3	3.2
Females	2.9	3.0	6.3

untary committee consisting of cardiac surgeons and cardiologists. The data come from all patients operated on for coronary artery disease in Australia plus their short-term outcome. Subsets of particular interest can be analyzed. No follow-up data are available.

The number of patients operated on from 1971 through 1980 and the decrease in mortality over this decade are listed in Table I. In 1980, >4,000 patients were operated on, with an operative mortality rate of 1.8%. All patients who had other procedures, such as valve replacement or coronary revascularization, are included. The number of grafts per patient has increased over the years and reflects common practice elsewhere in more complete revascularization (Fig. 1).

The number of operations for each of the 9 units in 1980 is shown in Table II. All but the first unit shown are in major teaching hospitals.

Australia is a commonwealth of 6 independent sovereign states, each with its own health service, medical education facilities, and specialist referral hospitals. Table III shows marked variation in the incidence of coronary artery surgery between the states. The rates are expressed as operations per million of population in 1974 and 1980. The number of patients operated on has increased markedly over 6 years, but the average

figure in 1980 was 234 per million. This rate is less than that of the United States—approximately 550 cases per million.

The indications for operation in 1980 are detailed in Table IV. Most patients were operated on for chronic stable angina. Operation on asymptomatic patients or for prognostic reasons was uncommon, about 1 in 200 patients. Reoperations for recurrent coronary artery disease accounted for 1.5% of the total.

Table V shows the ratio of patients with stable versus unstable angina operated on in each state and illustrates that medical and surgical practice varies in each state.

The severity of coronary disease in patients in 1980 is shown in Table VI. (Significant disease is defined as >70% vessel obstruction.) Seven percent were operated on for 1-vessel disease, 18% for 2-vessel disease, 57% for 3-vessel disease, and 18% for >50% left main disease. The operative mortality rate increases from 1-vessel to left main disease.

Table VII shows the number of grafts placed pe patient and th r respective mortality rates in 1980. Th reflects the ommon finding that the number of graf and the extent of additional procedures is usually re lated to mortality, except for valve replacement, whe coronary artery disease is often incidentally found a angiography.

The mortality rate by age and sex with revascula ization only and with the other procedures is shown i Table VIII. The mortality rate increases with ag women aged >60 years who have additional procedure have a higher mortality rate.

Overall, the indications for surgery and the results i Australia do not differ widely from those of othe Western nations. The Coronary Artery Surgical Reg ister of The National Heart Foundation is unique however, in that the number and distribution of a patients in the country who are operated on for coronar disease are known, and therefore, annual trends c changes in practice and mortality can be assessed.

Calcium-Entry Blockers and Cardiovascular Disease

PAUL M. VANHOUTTE, MD, and RICHARD A. COHEN, MD

The beneficial effects of calcium-entry blockers in the treatment of ischemia in the heart and in other tissues can be explained by (1) relaxation of venous smooth muscle, in particular that of the splanchnic veins; (2) negative inotropic effect on the myocardial cells; (3) negative chronotropic effects on the heart; (4) inhibition of vasospastic episodes in coronary and other large arteries; (5) depression of myogenic activity and responsiveness to vasconstrictor stimuli in precapillary resistance vessels; (6) inhibition of platelet aggregation; (7) possible increases in the deformability of hypoxic red blood cells; (8) protection of endothelial integrity and function; and (9) protection of the body cells, in particular myocardial cells, from prolonged exposure to anoxia and from massive entry of calcium during reperfusion. In the case of angina pectoris, the effects on the myocardial cells themselves, the decrease in preload and afterload, and the improvement of coronary perfusion combine to allow the heart to perform more work before an imbalance is reached between the metabolic demands of the myocardial cells and their blood supply. The increased myocardial performance may favor collateral circulation and withdrawal of the reflex load upon the heart, originating from the ischemic myocardium. The available calcium-entry blockers vary in their potency to affect the different components of the cardiovascular system.

To ensure cellular life, there must be a continuous stream of nutrients from the outside world to the extracellular space and a continuous stream of waste products from the cells to the outside world. This is achieved by the blood and the cardiovascular system, whereby the different components contribute to the functioning of the whole. The behavior of each component is influenced by events both upstream and downstream from it.[1] Whenever the cardiovascular system fails to meet the demands of an individual tissue, cellular intoxication with resultant depression of tissue function occurs. Stimulation of sensory nerves becomes unavoidable (Fig. 1); this results in ischemic pain and may trigger autonomic reflexes which further tax the system (Fig. 2). The pathophysiologic causes and consequences of ischemia are remarkably similar in different tissues (for example, heart, brain, limbs), but the resultant clinical picture depends on the specific function of each tissue. Thus, myocardial ischemia is particularly dramatic hemodynamically because of the central role played by the heart in providing the energy required to move the blood around the vascular tree to all the other tissues of the body. In most, if not all of the components of the cardiovascular system, calcium ions profoundly modulate cellular function. The pharmacologic actions of calcium-entry blockers permit us to understand why these substances may help restore the balance between the oxygen demands of and the blood supply to ischemic tissues and allow one to predict their beneficial effects in the treatment of cardiovascular disease.[2–16]

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Myocardial Ischemia

The beneficial effects of calcium-entry blockers in the treatment of angina pectoris[17,18] can be explained pharmacodynamically by the reduction in the amount of cardiac work or the improvement in perfusion of ischemic areas of the myocardium or both (Fig. 3). It is impossible to dissociate the actions of these drugs on the myocardium from those on vascular smooth muscle of the coronary and peripheral blood vessels.[2–4]

Work of the heart: The calcium-entry blockers can reduce cardiac work by:

(1) *Reducing the ventricular load.* By causing dilatation of the systemic veins, the calcium-entry blockers could reduce the *preload* of the ventricles.[1,19,20] To judge from the data available on isolated animal veins, these substances will affect mainly the splanchnic veins, which are a dynamic controller of the return of blood to the right atrium. Cutaneous veins appear to be less sensitive, which should ensure little interference by the calcium-entry blockers with the thermoregulatory and

orthostatic adjustments of the peripheral venous system.[6,7,14,15]

By inhibiting the myogenic tone of the precapillary vessels and decreasing their responsiveness to vasoconstrictor substances, the calcium-entry blockers reduce 1 of the major dynamic determinants of circulatory impedence, the systemic vascular resistance, and thus the afterload of the left ventricle.[1,21–23] These effects are most pronounced for substances such as verapamil and nifedepine, which explains their potential use as antihypertensive agents.[14]

Exaggerated entry of calcium into ischemic myocar dium may result in a slower rate of ventricular relaxa tion, resulting in an increased end-diastolic ventricula pressure[24]; by increasing the rate of relaxation, th calcium-entry blockers could decrease the load on th ventricular wall.

(2) *Decreasing myocardial contractility.* In vitro, a calcium-entry blockers have a negative inotropic effec

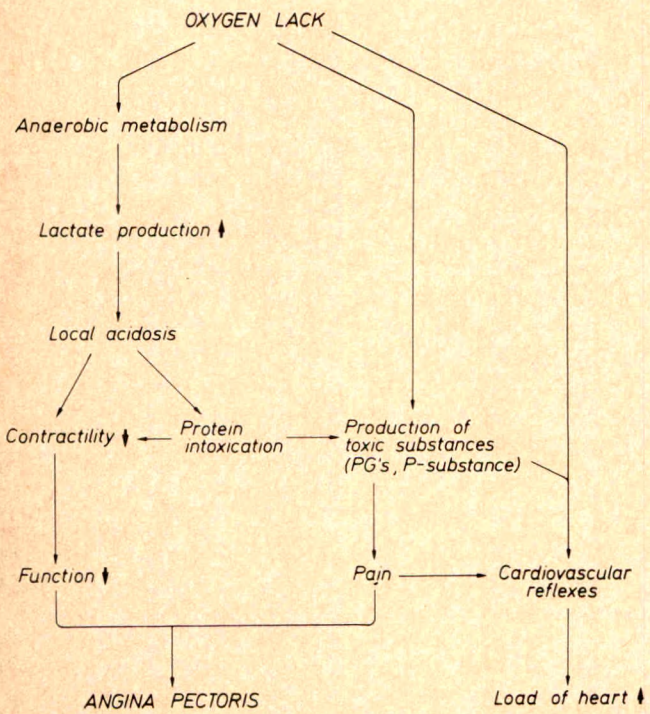

FIGURE 1. The consequences of tissue ischemia. The myocardium is taken as an example, but similar events occur in other tissues, such as skeletal muscle, leading to the combination of decreased function and pain perception (intermittent claudication). PG = prostaglandins. Reprinted from Vanhoutte[2] with permission of the publisher.

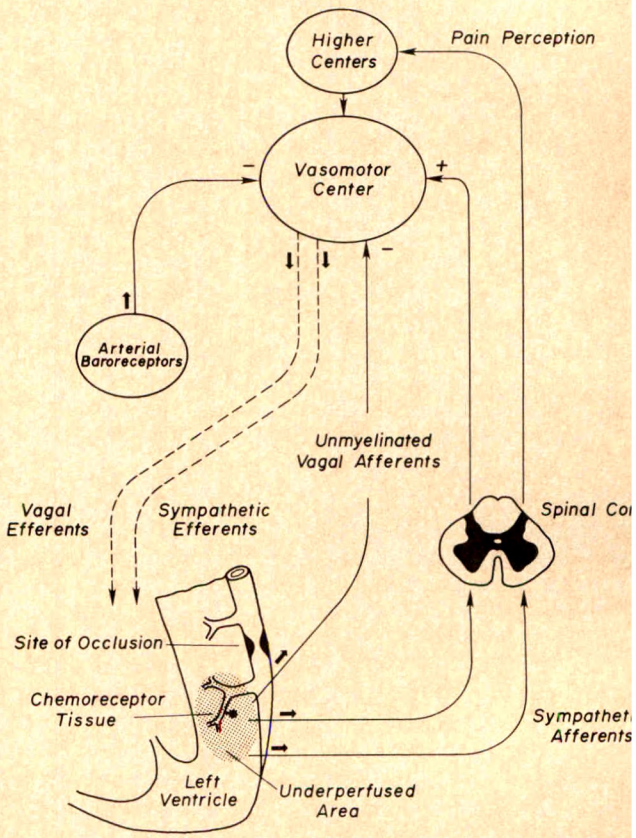

FIGURE 2. Factors involved in the cardiovascular reflex response t myocardial infarction. + activation; − inhibition. Courtesy of Dr. Joh T. Shepherd.

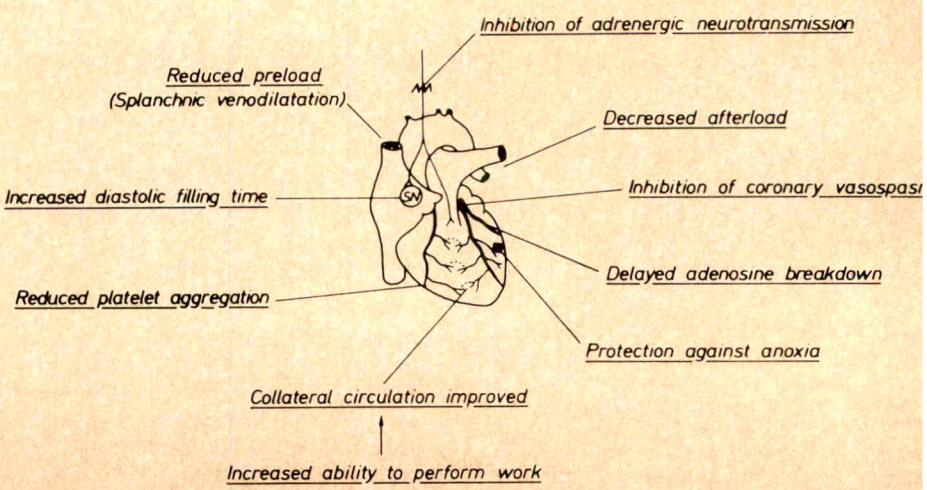

FIGURE 3. Effects of calcium-entry blockers that help explain their beneficial effects in the treatment of angina pectoris. Reprinted from Vanhoutte[2] with permission of the publisher.

however, important differences exist between the individual compounds in terms of their potency to decrease myocardial contractility versus their ability to inhibit vasoconstrictor responses of isolated blood vessels, in particular coronary arteries.[6,8,11,25–28] Thus, with compounds such as lidoflazine, myocardial depression is not observed in clinically effective doses.[16] Furthermore, in the intact organism, the negative inotropic effect of calcium-entry blockers can be counteracted by the reflex increase in sympathetic drive to the heart caused by reductions in systemic vascular resistance (e.g., nifedepine).[17,29]

Decreases in myocardial contractility undoubtedly reduce the imbalance between metabolic demands and oxygen supply in the heart, and thus can alleviate the symptoms of angina pectoris. However, this is attained at the cost of reducing the maximal potential of the heart to perfuse peripheral tissues at times of increased demands, and thus might limit muscular exercise.

(3) *Decreasing heart rate.* The negative chronotropic properties of the calcium-entry blockers vary, depending on their propensity to depress the generation and conduction of impulses in the specialized tissues of the heart, the reflex adjustment of sympathetic tone they induce, and their potency in inhibiting the release of the adrenergic transmitter by the adrenergic nerve terminals.[30] Clinical doses of some calcium-channel blockers decrease heart rate at intermediate work loads without affecting the maximal heart rate that can be achieved or myocardial contractility; higher values of cardiac output can be achieved at maximal loads.[11,12,28,30]

Coronary perfusion: Provided their effect on diastolic pressure is not marked, the calcium-entry blockers can theoretically improve coronary perfusion to the ischemic areas of the heart by:

(1) *Decreasing heart rate.* A reduction in heart rate at rest and during submaximal levels of exercise will prolong the diastolic filling time of the coronary circuit.[12]

(2) *Reducing wall tension.* A decrease in ventricular wall tension, whether due to improved relaxation of the myocardium or to a decreased external load (see section on "Work of the heart") will decrease the mechanical compression of the coronary microvessels, and thus improve coronary perfusion.

This may be particularly important in anoxic regions where calcium-entry blockers prevent the rigor of the myocardial cells due to exaggerated accumulation of intracellular calcium[28,31] and explain the redistribution of blood flow they cause from normally perfused to ischemic areas.[12,32,33]

(3) *Dilating coronary resistance vessels.* The calcium-entry blockers have a direct inhibitory effect on coronary vascular smooth muscle, and increase coronary blood flow at rest in the animal and in patients with angina pectoris.[22,25,26] In addition, compounds such as lidoflazine delay the breakdown of the endogenous coronary vasodilator adenosine.[8,12,14] The question of importance is whether or not the ability of the coronary resistance vessels to dilate is curtailed or if coronary arterioles are constricted to a greater degree than normal in ischemic regions of the heart. The calcium-entry blockers would have to preferentially vasodilate the ischemic regions to avoid a circulatory steal phenomenon toward the areas of the heart.[1,33] The data available on isolated coronary arteries suggest that conditions mimicking tissue ischemia, particularly the combination of a very low oxygen partial pressure, with high extracellular concentrations of potassium, cause profound constrictions of coronary vascular smooth muscle, and that these constrictions can be inhibited by calcium-entry blockers.[12–15]

(4) *Antagonizing coronary vasospasm.* In some patients with angina pectoris, spastic constriction of the large coronary arteries may be the primary cause of the myocardial ischemia (Prinzmetal's angina, variant angina), or may exacerbate the blood flow restriction due to a partial atherosclerotic obstruction of the coronary lumen.[17,34,35] Although the cause of such coronary spasm is unknown, the clinical evidence that calcium-entry blockers can prevent it is convincing. Nifedipine prevents an abnormal coronary vasoconstriction in response to the cold pressor test in patients with coronary artery disease who are taking propranolol.[36] In vitro work on large animal coronary arteries demonstrates that these compounds inhibit constrictions caused by several possible mediators of coronary vasospasm or by ergonovine maleate, which is used diagnostically to induce coronary spasm.[8,12–14]

(5) *Augmentation of collateral flow.* Data from animals suggest that calcium-entry blockers such as lidoflazine and diltiazem accelerate the normally occurring phenomenon of collateralization; this improvement of collateral formation is probably a consequence rather than a cause of the improved cardiac function and of the resulting ability to increase physical activity.[12,33,37]

The net result of treatment with a given calcium-entry blocker will also depend on the time course of action of the drug. Thus, agents with acute and pronounced vasodilator properties in systemic arterioles and veins (e.g., nifedepine) will cause an almost instantaneous unloading of the heart, similar to that obtained with nitrates. With more slowly acting drugs (e.g., lidoflazine), the immediate hemodynamic effects of clinical doses may not be so obvious. However, as the condition of the ischemic myocardium improves over time, diseased cells regenerate and can perform more work. The reflex vasoconstriction (Fig. 2) originating in the ischemic myocardium decreases, and more of the improved energy-generating potential of the heart can be used to meet the demands of metabolically active tissues.

Other Tissues

Provided the pressure generated by the heart is maintained at an appropriate level, the amount of blood delivered to each tissue will depend on the resistance flow it offers, and thus mainly upon the diameter of its blood vessels and the viscosity of the blood. In normal conditions, the degree of opening of the arterioles is governed by the metabolic needs of the tissues surrounding them, which ensures an appropriate blood supply.[1,38,39] There is no evidence that in abnormal

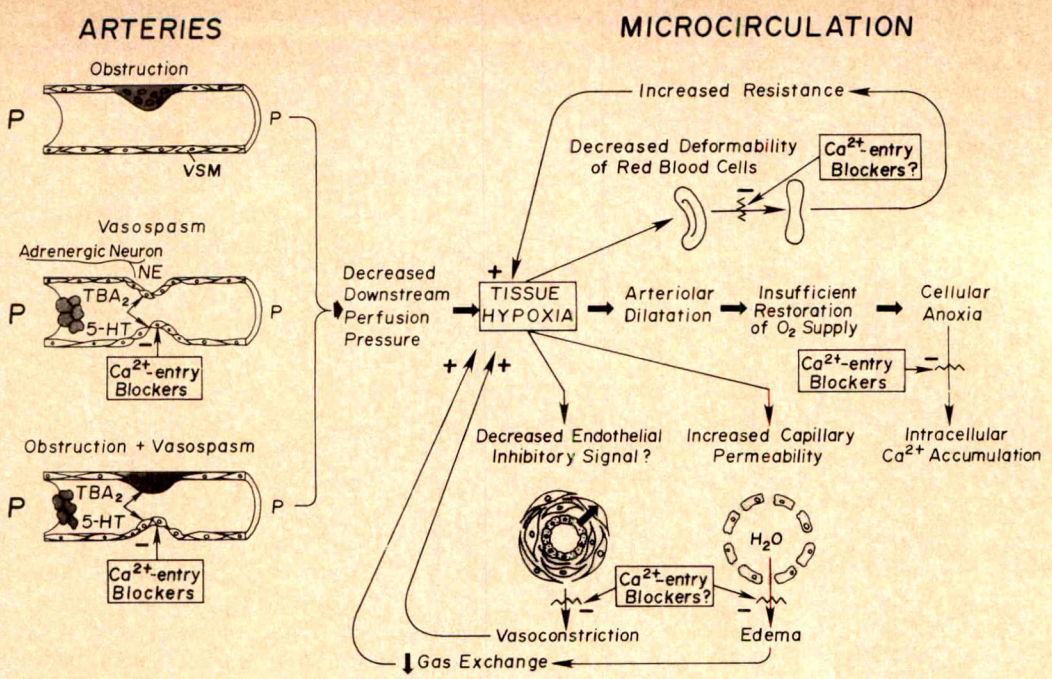

FIGURE 4. The events leading to and maintaining tissue ischemia, with indication of the possible sites of action of calcium-entry blockers. P = blood pressure; VSM = vascular smooth muscle; 5-HT = 5-hydroxytryptamine. Reprinted from Vanhoutte[5] with permission of the publisher.

conditions the precapillary resistance vessels lose the ability to dilate in response to the metabolic demands of the tissues that they subserve. However, in certain forms of arterial hypertension, an arteriolar constriction may contribute to the origin or the maintenance of the disease; in those cases, calcium-entry blockers, particularly those that affect the myogenic activity of vascular smooth muscle most, have antihypertensive properties.[14] Ischemia of peripheral tissues, including the brain, occurs mainly when the diameter of a large artery is reduced and if the collateral circulation is insufficient to meet the demands of the active tissue. If the restriction of the blood flow to an organ is due solely to mechanical obstruction (for example, atherosclerosis, embolism, external compression), no primary beneficial effect is to be expected from calcium-entry blockers, or from other types of vasodilator drugs; in contrast, vasodilator treatment may result in further restriction of the blood flow to the ischemic tissues because the drugs cause a decrease in resistance in normally oxygenated beds (steal phenomenon).[1,40]

However, obstruction can be due to spasm of the vascular smooth muscle of the arterial wall, as may be the case in cerebral arteries in migraine headache or in digital arteries during episodes of Raynaud's phenomenon. Other arteries also contain substantial amounts of vascular smooth muscle cells and, at least in vitro, react strongly to vasoconstrictor substances.[13,14,16,41] In all arterial smooth muscle studied so far, calcium-entry blockers have been shown to be potent inhibitors of the contractile responses evoked by a variety of vasoconstrictor substances; thus, one can predict that they will be effective in antagonizing arterial vasospasm not only in the coronary circulation (see "Coronary perfusion"), but also in other vascular beds.[2–5,13,14,42–44]

Another dynamic determinant of the resistance to flow is the viscosity of the blood; hyperviscosity has been proposed as 1 factor in peripheral circulatory disturbances. The viscosity of the blood is determined in part by the deformability of the red blood cells; this deformability is of critical importance at the microcirculatory level, where the erythrocytes must travel through capillaries with a diameter smaller than their own. Metabolic deprivation markedly reduces red blood cell deformability, which theoretically should increase the apparent viscosity of the blood in the precapillary vessels and, thus, the resistance to flow, and may further reduce proper oxygenation of the tissues.[1,13,45,46] Certain calcium-entry blockers can reduce the viscosity of hypoxic blood; this could explain, in part, a beneficial effect on peripheral vascular insufficiency,[45,46] although in vitro demonstration of such effects often requires suprapharmacologic concentrations.[46] Another possible reason for mechanical hindrance of blood flow at the microcirculatory level is the occurrence of platelet aggregates; certain calcium-entry blockers have strong antiaggregating properties[12] (Fig. 4).

In contrast to the heart, and with the exception of skeletal muscles engaged in isometric contractions, the tissue pressure in peripheral organs usually is not considered to be an important determinant of the resistance to flow at the microcirculatory level. Tissue pressure may limit blood flow in edematous tissues, where exaggerated extravasation of fluid occurs when capillary permeability increases. It has been suggested that such

increased permeability may be caused by the contraction of actomyosin-like proteins in the endothelial cells, which widens the pores of the capillary membrane; contraction of the endothelial cells facilitates their desquamation and their appearance in the peripheral blood.[47] Certain calcium-entry blockers have long been known to decrease peripheral edema formation,[12] and the calcium-entry blockers tested so far reduce the number of circulating endothelial cells.[47]

Conclusion

Most of the proposed therapeutic effects of calcium-entry blockers in cardiovascular disease can be related to their effects on the function of the contractile cells located in the heart and the vascular wall; their effects on the formed elements of the blood are still a matter of discussion. It should be emphasized that even if the direct interference of calcium-entry blockers with the contractile process in cardiac and vascular muscle cells fails to restore an appropriate blood flow to ischemic areas, these substances will prevent exaggerated influx of extracellular calcium during and after the ischemic episodes, and thus protect the tissue cells against some of the most deleterious effects of oxygen deprivation and the most damaging events in the early stages of reperfusion. Although this has been documented best in the myocardium,[28,31] it can be expected that a similar protective effect against anoxia can be obtained in other tissues (e.g., brain) as well. Finally, the reduction in the degree of desquamation of the endothelial cells observed with most calcium-entry blockers, and the inhibition of platelet aggregation caused by some of them, should not only reduce the release of vasoconstrictor substances (such as 5-hydroxytryptamine or thromboxane A_2, which may be a factor in arterial vasospams) from platelets aggregating at endothelial lesions, but may also slow the progression of the atherosclerotic process in both coronary and systemic arteries.[1,48,49] In that regard, it is interesting to note that the calcium antagonist lanthanum prevents atherosclerosis in animal models of the disease.[50]

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Beta-Adrenoceptor–Blocking Drugs: Current Status and the Significance of Partial Agonist Activity

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There is some evidence that partial agonism is an important property of beta-blocking drugs, and this property may be exploited to produce a new range of positive inotropic drugs. With the established beta-adrenoceptor–blocking drugs, the level of partial agonist activity is weak and the dose-response curve for this property is shallow. However, its absence appears to increase the likelihood of inducing bronchospasm and bradycardia, and drugs that lack intrinsic sympathomimetic activity appear more likely to be associated with rebound cardiac arrhythmias on cessation of treatment. The idea of a small level of hormone activity—in this case catecholamine activity—being necessary to maintain normal cardiac and perhaps bronchial function is not new. Minimal doses of steroids are essential to maintaining the inotropic action of cardiac muscle. There is now enough accumulated evidence to suggest that a minimal degree of beta-adrenoceptor stimulation is also important for normal bronchial and cardiac function, and its absence increases the incidence of bradycardia and the risks of bronchospasm and rebound arrhythmias.

The use of the terms alpha and beta adrenoceptors for describing catecholamine receptors is now generally accepted. Beta adrenoceptors occur in a variety of sites, including blood vessels, heart, brain and kidneys; drugs that act on these receptors can modify not only cardiovascular disorders such as angina, high blood pressure and the cardiac arrhythmias, but also diseases such as asthma, thyrotoxicosis and migraine.

There are at least 2 types of beta adrenoceptors, $beta_1$ and $beta_2$, and tissues vary in their receptor complement. For clinical purposes, it is reasonable to use the classification listed in Table I. However, tissues such as heart, which contain predominantly $beta_1$ adrenoceptors, also contain some $beta_2$ adrenoceptors; consequently, selectivity is not absolute.[1]

Structurally, the beta-blocking drugs are modifications of the beta-adrenoceptor stimulant isoprenaline. They consist of an isoprenaline-like side chain with a different aromatic nucleus. When isoprenaline attaches to the beta adrenoceptor on the membrane surface, a number of specific linkages are involved. Each linkage is actually a weak bond; these bonds are formed rapidly, but are also easily broken. The highly specific way in which isoprenaline attaches itself to the receptor results in maximal activation of the receptor, which is believed to be linked to adenylate cyclase.[2]

The attachment of the blocking drug to the receptor resembles that of isoprenaline, but there are important differences. The attachment to the receptor results in less or no activation of adenylate cyclase and prolonged occupation of the receptor results in blockade. The mechanism of the occupation is uncertain, but it is known that these compounds compete with isoprenaline and other beta agonists for the receptor.

Classification

Beta-adrenoceptor–blocking drugs differ in 3 clinically important respects: intrinsic sympathomimetic activity, cardiac selectivity and bioavailability. The

TABLE I Classification of Tissue Beta Adrenoceptors

Tissue	Type of Receptor
Heart	$Beta_1$
Lung	$Beta_2$
Peripheral blood vessel	$Beta_2$
Central nervous system	$Beta_1$,$beta_2$
Metabolic receptors	Usually $beta_2$, but many are unclassified

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membrane-stabilizing properties of these compounds usually occur at doses greater than those used in clinical practice.[3] These drugs can be classified in 2 ways: in terms of their selectivity for beta-adrenoceptor subtypes and according to the degree of intrinsic sympathomimetic activity that they possess. The frequently used nonselective compounds include drugs without intrinsic sympathomimetic activity, such as propranolol, timolol, nadolol and labetalol. Labetalol can also block alpha adrenoceptors. Oxprenolol, alprenolol and pindolol are nonselective drugs that possess intrinsic sympathomimetic activity.

Cardioselective drugs without intrinsic sympathomimetic activity include metoprolol, atenolol and bevantolol. Practolol is cardioselective and has intrinsic sympathomimetic activity. Acebutolol has weak intrinsic sympathomimetic activity and is cardioselective in animals, but not in man.

Intrinsic sympathomimetic activity: Intrinsic sympathomimetic activity is a property that has, in the past, been somewhat neglected; however, interest has been rekindled by reports that drugs with this property are less likely to induce bronchospasm and have a lower incidence of adverse effects, such as Raynaud's phenomenon.[4,5] There have also been reports that rebound cardiac arrhythmias may follow abrupt withdrawal of beta-adrenoceptor blockers with weak or absent intrinsic sympathomimetic activity.[6,7]

The first beta-adrenoceptor–blocking drug, dichloro-isoprenaline, had potent intrinsic sympathomimetic activity and increased the resting heart rate.[8] Clearly, the greater the positive inotropic action, the more likely this is to occur. However, available beta-adrenoceptor–blocking drugs with intrinsic sympathomimetic activity, such as pindolol, oxprenolol, alprenolol and acebutolol, have much less stimulant activity (Table II). The dose-response curves for the partial agonist property of these drugs is shallow and the inotropic action so weak that the net effect in man is to prevent the extreme effects of beta-adrenoceptor blockade, rather than to produce a positive inotropic effect. Moreover, the property does not interfere with their potency as beta-adrenoceptor–blocking agents, as they are equally effective in blocking exercise-induced tachycardia[9]; it merely reduces the effects of negative inotropism on tissues such as heart and lung.[10–12]

Thus, under resting conditions, heart muscle is under sympathetic stimulation and the complete absence of sympathetic activity may, on occasion, lead to bradycardia, cardiac failure and conduction defects.[11] Similarly, the absence of sympathetic activity in the bronchi may increase the percentage of the population that develops bronchospasm and increase the likelihood of patients with asthma developing an exacerbation of symptoms.[4,13]

Positive inotropic drugs: A new range of compounds which are partial beta-adrenoceptor agonists with significant positive inotropic properties have become available for clinical trials in various forms of cardiac insufficiency. These drugs include the cardioselective agonist dobutamine and the partial agonists prenalterol and ICI-118,587.[14–16] Prenalterol and ICI-118, 587 are structurally similar to the beta-adrenoceptor–blocking agents and have 20 to 60% of the maximal inotropic effect of isoprenaline. However, at high doses their blocking properties become more prominent and prevent further stimulation of the heart.

TABLE II Relative Degree of Intrinsic Sympathomimetic Activity (ISA) of Several Frequently Used Beta-Adrenoceptor–Blocking Drugs

Drug	Relative Degree of ISA
Dichloroisoprenaline	+++
Pindolol	++
Oxprenolol	+
Alprenolol	+
Acebutalol	+
Practolol	+
Propranolol	0
Timolol	0
Metoprolol	0
Atenolol	0
Nadolol	0
Labetalol	0

In heart failure, safe, selective, positive inotropic drugs could well be of value in improving cardiac performance. In the conscious animal, such compounds produce little increase in heart rate, presumably because their administration is associated with some increase in vagal activity and their blocking properties reduce the incidence of arrhythmias. The present group of partial agonists can only be given parenterally, but it is expected that orally bioavailable drugs of this type will soon become available; the hope is that they will be safe and effective in patients with chronic cardiac failure.

It would seem, therefore, in designing a beta-adrenoceptor–blocking drug with or without partial agonist activity, that many options are available, ranging from no activation of the receptor to full activation of the receptor. When the degree of activation is small and comparable in amount to resting endogenous sympathetic activity, the term *intrinsic sympathomimetic activity* has been invoked. It is, however, merely one end of the spectrum of partial agonism.

Extracardiac adverse effects: The extracardiac adverse effects of beta-adrenoceptor–blocking drugs include bronchospasm, aggravation of chronic bronchitis, abnormal dreams, nightmares and Raynaud's phenomenon. Beta-adrenoceptor–blocking drugs also have the usual incidence of gastrointestinal adverse effects, weakness and tiredness. One difficulty in assessing the value of intrinsic sympathomimetic activity in modifying the incidence of such adverse effects is the lack of sufficiently large clinical trials that compare drugs with and without this property. A similar problem affects the assessment of the value of cardioselectivity. Overall, the frequency of most extracardiac adverse effects is similar to that produced by nonselective agents. This suggests either that the current drugs are not very selective or that $beta_1$ adrenoceptors are widely distributed through the body.

Bronchospasm: Shortly after its introduction, it was found that propranolol could cause severe bronchospasm in asthmatic patients.[7] Stimulation of $beta_2$-adrenoceptors in normal bronchi leads to smooth muscle relaxation, and reduction in adrenoceptor activity seems to aggravate asthma and may even induce asthma in some patients with little or no history of chronic respiratory problems. There is some evidence in both animals and humans to suggest that drugs that lack intrinsic sympathomimetic activity are more likely to precipitate these asthmatic problems. Oh et al[18] have demonstrated that during an exercise challenge, patients pretreated with propranolol have greater airway obstruction than patients treated with pindolol or oxprenolol.

In comparative clinical trials, Morgan et al.[4] have reported a higher incidence of bronchospasm during treatment with propranolol and timolol, which lack intrinsic sympathomimetic activity, than during treatment with pindolol and alprenolol, which possess intrinsic sympathomimetic activity. In other studies,[19] patients whose lung function deteriorated with propranolol showed no deterioration with pindolol during acute and chronic treatment. There is considerable evidence that the cardioselectivity of drugs such as practolol, atenolol and metoprolol is only relative and may be lost at higher therapeutic doses.[20] If a patient does develop bronchospasm with a beta-adrenoceptor–blocking drug, however, there is evidence to suggest that $beta_2$-adrenoceptor agonists more easily reverse the bronchospasm during treatment with a cardioselective agent.[20,21] However, because all of these drugs are competitive antagonists, larger doses of salbutamol will reverse the bronchospasm induced by the more potent nonselective agents.[22]

These data should not be taken to mean that it is safe to use any of these particular groups of drugs in known asthmatic patients. All beta-adrenoceptor drugs, including the present range of cardioselective beta antagonists, can precipitate severe bronchospasm (sometimes fatal) in asthmatics and can interfere with the drug treatment of asthma.[23]

Given the widespread use of this class of drug, what is of concern is the precipitation of bronchospasm in patients without a clear-cut history of asthma. Although most patients show no deterioration in lung function during treatment with beta-adrenoceptor–blocking drugs, patients with no history of asthma have developed bronchospasm when they take drugs without intrinsic sympathomimetic activity; that is, the absence of sympathomimetic activity seems to increase the risk of bronchospasm. These data suggest that the presence of intrinsic sympathomimetic activity and cardioselectivity may both be important protective properties which will reduce the incidence of adverse bronchial effects of beta-adrenoceptor–blocking drugs in a population in which the asthmatic patients have been excluded from treatment. These suggestions require investigation by large-scale clinical trials.

Raynaud's phenomenon: Cold extremities and aggravation of the symptoms of Raynaud's phenomenon and peripheral vascular disease are the most frequently reported adverse reactions associated with the use of beta-adrenoceptor–blocking drugs.[24] Aggravation of peripheral vascular disease is often insidious. The patient may present with incipient gangrene of the toes months after the commencement of therapy.[25] In some cases, a history of peripheral vascular disease may not be elicited because the patient cannot walk far enough to develop claudication. The mechanism of this adverse effect is not clearly understood, but the decrease in cardiac output and the increase in peripheral resistance that frequently occur with this group of drugs probably contributes. Drugs with intrinsic sympathomimetic activity have lesser effects on resting cardiac output and have been reported to produce a lower incidence of cold extremities and Raynaud's phenomenon.[5] However, the data are not unequivocal, and Raynaud's phenomenon is seen with all beta-adrenoceptor antagonists. The drugs as a group are contraindicated in peripheral vascular disease.

Cardiac adverse effects: All beta-adrenoceptor–blocking drugs block the heart at least a little and reduce exercise-induced tachycardia. Drugs such as propranolol and timolol, which lack intrinsic sympathomimetic activity, do this to a larger extent than drugs like pindolol and oxprenolol, which possess intrinsic sympathomimetic activity.[4] In a comparative study in hypertensive patients, metoprolol and atenolol (2 cardioselective drugs that lack intrinsic sympathomimetic activity) were shown to have a 30% incidence of significant bradycardia, defined as the development of pulse rates of <55 beats/min; some patients had heart rates <50 beats/min.[10] The negative inotropic properties of beta-blocking drugs are also known to contribute to the cardiac failure that can develop, particularly in elderly patients, during treatment with beta-adrenoceptor–blocking drugs. Whether drugs with intrinsic sympathomimetic activity, which have fewer negative inotropic effects, are less likely to induce cardiac failure is not certain.

Also of concern are reports of rebound arrhythmias that occur upon withdrawal of treatment with beta-adrenoceptor–blocking drugs. Miller et al[6] reported a series of 20 patients with angina treated with propranolol who subsequently stopped treatment. Six of these patients had serious myocardial events: 1 died suddenly, 1 had a myocardial infarction, another developed ventricular tachycardia, and 3 developed coronary insufficiency.

Many adverse cardiac events have been reported after cessation of therapy with beta-adrenoceptor–blocking drugs, but almost all have involved drugs with little or no intrinsic sympathomimetic activity. Ross et al[7] have reported that these drugs produced hypersensitivity of beta-adrenoceptors and cessation of treatment results in rebound tachycardia during exercise. Prichard et al (personal communication) demonstrated a similar rebound tachycardia with propranolol and atenolol, but not with pindolol. These data suggest that a certain level of intrinsic sympathomimetic activity may protect against the development of withdrawal effects.

Metabolic effects: Release of insulin from the beta cells of the pancreas is increased by beta-adrenoceptor

agonists and reduced by alpha-adrenoceptor agonists.[26] The beta adrenoceptors involved have been identified as mainly of the $beta_2$ type.[27] However, these adrenoceptors probably play only a relatively minor role in regulating glucose homeostasis. Evidence for this includes the minimal effect of an intravenous infusion of an alpha- or a beta-adrenoceptor–blocking drug on resting insulin levels[28] and the small effect of beta-adrenoceptor–blocking drugs on glucose tolerance.[29] Alpha and beta adrenoceptors also have little direct effect on the release of pancreatic glucagon.[30]

In other areas of glucose homeostasis, the sympathetic nervous system appears to play a greater role. During hypoglycemia for example, adrenaline and noradrenaline stimulate hepatic glycogenolysis and gluconeogenesis, leading to a normalization of the blood sugar level.[31] Although this effect is believed to be mediated mainly through hepatic alpha adrenoceptors,[32] several studies have shown that beta-adrenoceptor–blocking drugs can delay the recovery of the blood sugar level in normal volunteers after challenge with insulin.[33–35] Beta adrenoceptors may play some role in the process, or else propranolol hinders hepatic glucose production indirectly, perhaps by reducing the blood lactate response to hypoglycemia or by blocking glycerol release.[35,36] In studies in normal volunteers, the recovery of the blood sugar level has been more rapid in subjects given $beta_1$-selective agents,[33,37] and this is one reason why their use has been advocated in diabetic patients liable to hypoglycemia.

However, the generalization of results from normal volunteers to diabetic patients might not be warranted. In a recent study comparing the effects of oxprenolol, metoprolol and placebo on the hypoglycemic response to insulin, the rate of plasma glucose recovery after hypoglycemia was found to be grossly impaired in diabetic patients and unaffected by treatment with beta-blocking drugs.[38] Hypoglycemic symptoms were also similar in the placebo and drug-treated groups, although sweating was more frequent in those taking the beta-adrenoceptor–blocking agents.

Nevertheless, the choice between $beta_1$-selective and nonselective drugs in diabetic patients prone to hypoglycemia may still be important by virtue of their differing effects on the cardiovascular responses to hypoglycemia. With propranolol and other nonselective compounds, both systolic and diastolic pressure may increase sharply, presumably as a consequence of unopposed alpha-adrenoceptor stimulation[37] in association with excessive sympathetic activity. In studies with $beta_1$-selective agents, this effect is less pronounced.[37,38]

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Beta Blockers in Ischemic Heart Disease

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Many trials have reported that beta blockers increase survival after myocardial infarction; these trials are reviewed. The timolol trial was randomized and showed that mortality was reduced for all patients randomized to beta blockers. Similar findings have been found in both the metoprolol trial in Göteburg and the Beta-Blocker Heart Attack Trial in the U.S. Chronic beta-blockade therapy appears to reduce mortality in patients who survive acute myocardial infarction. The mechanism is as yet unknown.

Myocardial infarction (MI) is a major cause of death in the Western world. Approximately 50% of all deaths in men aged 50 to 64 years are caused by cardiovascular diseases. Most deaths occur outside the hospital. The high incidence of MI has initiated different intervention studies. The first clinically useful beta blocker, propranolol, became available in 1964. Shortly thereafter, Snow[1] published an open study with propranolol in 93 patients after acute MI, showing a significant mortality reduction. Many trials since then have evaluated the effect of beta-blockade on survival both during the acute MI and during the long-term follow-up. The methods of the trials have been refined during the last decade. Many well-controlled trials have shown that beta blockade may reduce long-term mortality in MI patients. In the last year, total mortality has been reduced after acute administration of beta blockers. This report reviews the role of beta blockers in ischemic heart disease.

Prospective Randomized Trials

Since the late 1960s, retrospective and prospective trials have reported an increased survival among patients with MI. Several trials are inconclusive, and most did not contain a representative group of patients[2–5] (Table I). One with too few patients had too few end points to produce meaningful results.[2] In the study by Barber et al,[6] a high oral dose of practolol was administered as soon as possible after the onset of symptoms. There was no significant difference between placebo and practolol treatment. However, in 1 retrospective analysis, patients with fast heart rates on entry seemed to have an improved survival. If sudden death is used as a major end point, the late mortality rate is somewhat lower in the practolol group.

The first positive trial was published from our center in 1974, and several large and well-conducted studies have documented the positive effect of long-term beta blockade in patients with MI since (Table II). In the Gothenburg alprenolol study, 230 patients from 57 to 67 years of age were separated into 4 different risk groups.[7,8] In each separate group, the patients were randomly allocated to treatment with either 400 mg/day of alprenolol or placebo. After inclusion, only 8 patients were withdrawn from the placebo and 8 from the alprenolol groups. None of these patients died or had a reinfarction before the completion of the follow-up. The prospective stratification was successful in that there were no deaths in the low-risk group receiving either placebo or alprenolol. Thus, the reduction of the number of sudden deaths was statistically significant when this difference was analyzed for relevant combinations of groups (Fig. 1). Total mortality was reduced by 50%. The number of nonfatal reinfarctions did not differ between the alprenolol and placebo groups. This study has been criticized for 3 major reasons: the small number of patients in the study and, therefore, a too low level of statistical power; a high frequency of digitalis treatment; and the lack of statistical significance for the

TABLE I Inconclusive Prospective Postinfarction Trials

Study	Year	Patients (n)	Compound (mg/day)
Barber et al[6]	1975	484	Practolol (600)
Wilcox et al[3]	1980	388	Atenolol (100) Propranolol (120)
Wilcox et al[4]	1980	473	Disopyramide (450) Oxprenolol (120)
Baber et al[5]	1980	720	Propranolol (120)

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TABLE II Characteristics of the Positive Completed Long-Term Study Results With Beta Blockers

Study	Published	Active drug (mg/day)	Start After MI (days)	Duration (months)	Ages (years)	Patients (n)	Cumulative Placebo Mortality (%)	Reduction of Total Mortality (%)	Reduction of Reinfarction (%
Wilhelmsson et al	1974	Alprenolol (400)	35–56	24	57–67	230	12	50	11
Multicenter International	1975 1977	Practolol (400)	7–30	12–36	<70	3053	8*	20	23
Andersen et al	1979	Alprenolol (10 iv; 400)	"Acute"	12	All	282	20	55	—
Norwegian Study	1981	Timolol (20)	6–27	12–36	20–75	1884	22	39	28
Hjalmarson et al	1981	Metoprolol (15 iv; 200)	"Acute"	3	40–75	1395	9	36	35
Beta-Blocker Heart Attack Trial	1981	Propranolol (180–240)	5–21	12–30	30–69	3837	10	26	. . .
Hansteen et al	1982	Propranolol (160)	4–6	12	35–70	560	13	32	24

* Total mortality.
IV = intravenous.

effect on total mortality. Although small, the group of patients under study was representative of all the infarction cases in Göteborg. It has been suggested that alprenolol may act only by reducing fatal digitalis-induced ventricular arrhythmias, but information about digitalis is not available from other trials. Digitalis and alprenolol may have a synergistic effect, thus decreasing fatal ventricular arrhythmias. The prevalence of digitalis treatment is unlikely to have any significant effect, since the long-term mortality rate in Sweden is the same as that in other European countries. Also, the prevalence of digitalis treatment was the same among survivors and among those who died in both alprenolol and placebo groups.

In many countries, specific or mode-specific mortality as end points are difficult to use due to the uncertain causes of death when the autopsy rate is low. In Gothenburg, the autopsy rate was high (90%). Alprenolol was unlikely to affect noncardiac deaths. There fore, the difference for total mortality is less than tha for sudden cardiac mortality, and the reduced sudde death rate implies a meaningful reduction of tota mortality.

The Multicentre International Practolol Trial[9,1] clearly demonstrates a difference regarding both sudde and cardiac mortality among patients in the stud (Table III). The low placebo mortality rate reflects tha the patients were not representative of all postinfarctio cases. Pretrial exclusions were not detailed and thes findings cannot be used to generalize. No prognosti stratification was used. A retrospective analysis wa carried out in order to define target patients with maximal benefit from treatment with practolol. Th analysis indicated that low body weight, low prerar domization diastolic pressures and site of infarctio were important variables in selecting patients. Ther was an excessive number of early deaths in the practo lol-treated patients who had inferior infarctions. Bod weight was inversely correlated with practolol plasm levels, suggesting a dose-response relationship. A defec of such a retrospective analysis is that it may not be basis for therapeutic recommendation, but help to in tiate new trials that have to use prognostic stratificatio For all randomized patients, practolol did not signif cantly reduce the total mortality, which is probably du to the high mortality among the patients withdraw from the study.

The aim of the Copenhagen trial[11] was to study shor and long-term mortality as well as tolerance for alprer

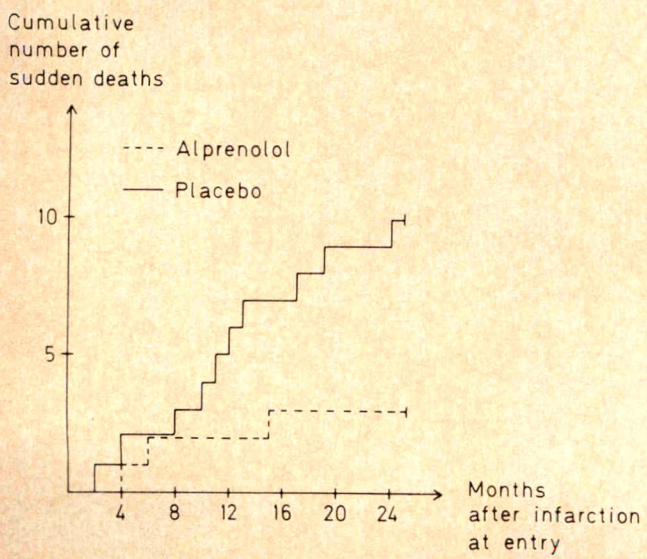

FIGURE 1. Cumulative number of sudden deaths in the groups treated with alprenolol and placebo. Reproduced from Vedin et al[8] with permission of the publisher.

TABLE III End Points in the Multicentre International Trial of Practolol

	Placebo	Practolol	p value
Patients (n)	1520	1533	. . .
Total deaths	127	102	NS
Cardiac deaths	78	48	<0.01*

* p values for patients continued in trial; 421 were withdrawn fro placebo and 437 from practolol.

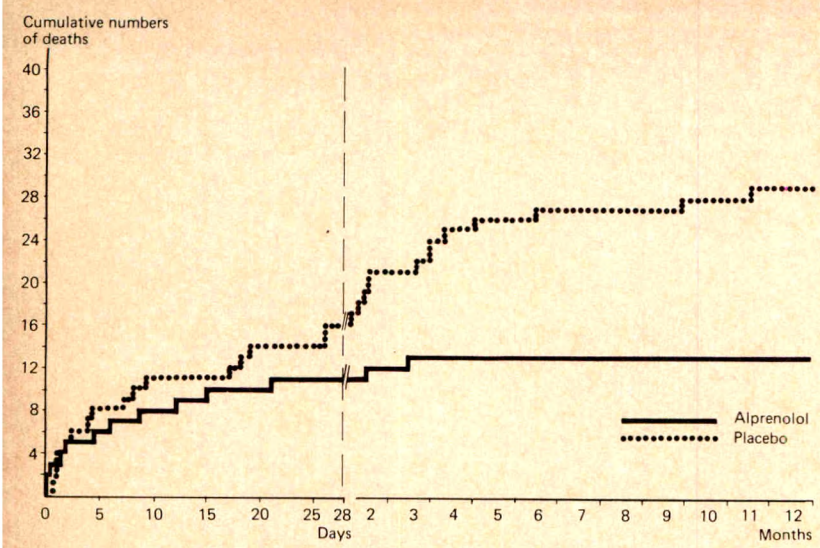

FIGURE 2. Cumulative number of deaths in all patients >65 years treated with alprenolol or placebo during the year of treatment. Reproduced from Andersen et al[11] with permission of the publisher.

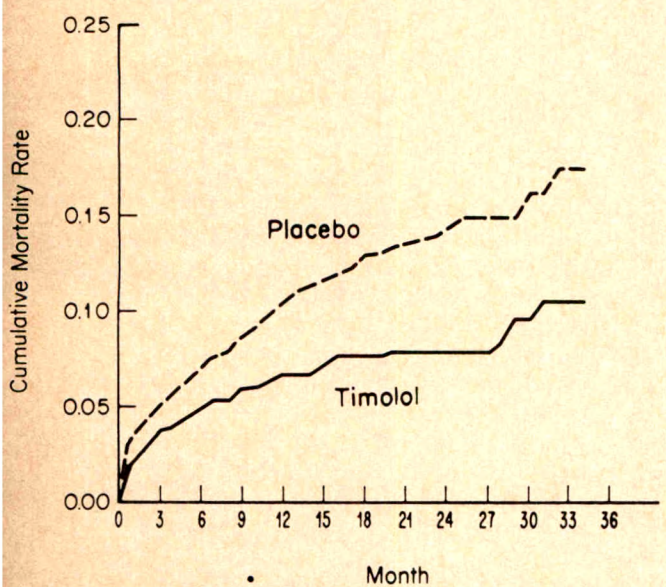

FIGURE 3. Life-table cumulative rates of deaths from all causes. Reproduced from the Norwegian Multicenter Study Group[12] with permission of the publisher.

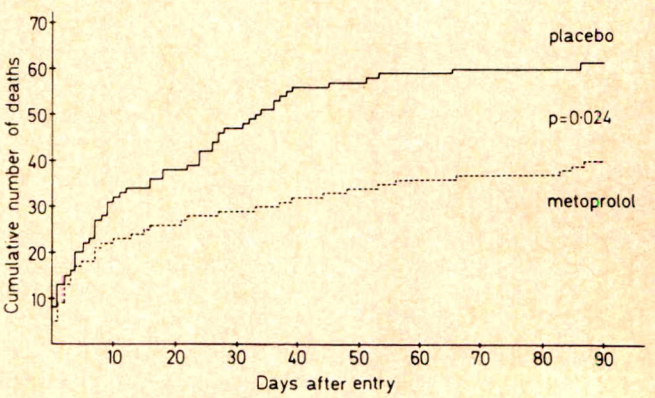

FIGURE 4. Cumulative number of deaths in all patients randomly allocated to treatment with metoprolol and placebo. Reproduced from Hjalmarson et al[13] with permission of the publisher.

olol in elderly patients. Treatment was begun on admission to the coronary care unit, when patients were allocated randomly to treatment with intravenous alprenolol or placebo. Oral maintenance treatment ensued and the patients were followed for 1 year after admission. Prognostic stratification was made on the basis of age, heart rate and degree of impaired consciousness at admission. Pretrial exclusions have been detailed. In patients <65 years, treatment and placebo groups were comparable. In patients >65 years, the placebo group was biased toward a worse prognosis than the alprenolol group. For all randomized patients, total mortality was reduced among those <65 years (Fig. 2). In patients with a diagnosis of definite myocardial infarction, mortality was reduced for the short-term (28 days) period; this was not true for all randomized patients. Ventricular arrhythmias and creatine phosphokinase release were reduced among the alprenolol patients, particularly if treatment was instituted soon after onset of symptoms. The findings were different in patients >65 years. Patient intake in this age group was stopped for ethical reasons. There was no difference between alprenolol and placebo regarding the total mortality. The outcome in the placebo group may be partly expected, based on the high number of previous infarctions. In patients with first infarctions, mortality was not reduced. Overall, the excess mortality was explained by a combination of a history of MI and signs of unstable circulation on admission but before randomization.

The Norwegian timolol trial,[12] designed by our group, showed that total mortality was reduced for all randomized patients and also for all presented subsets of patients. The design was stratified and the numbers were large. The patients were representative of a general population, and all pretrial exclusions have been clearly presented. Mortality data for patients excluded before randomization will become available. The groups were

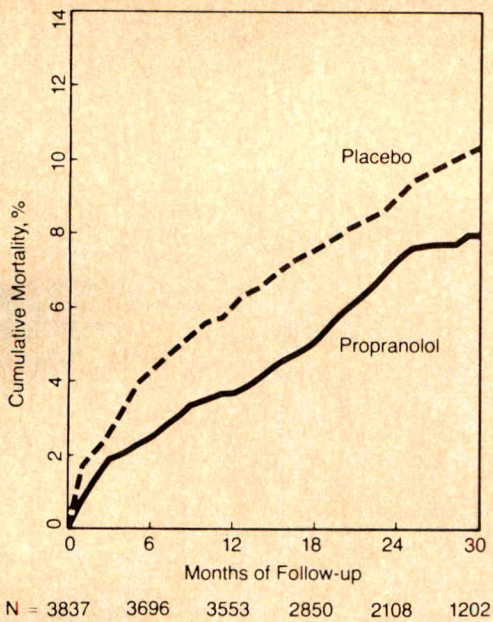

FIGURE 5. Life-table cumulative mortality curves for propranolol and placebo. Reproduced from the Beta-Blocker Heart Attack Study Group[14] with permission of the publisher.

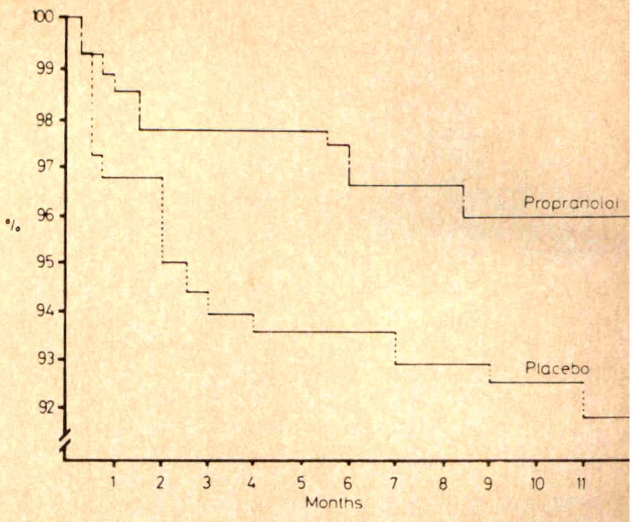

FIGURE 6. Life table for cumulative sudden death rate. Reproduced fro Hansteen et al[15] with permission of the publisher.

reasonably balanced and analyses ascertained that the small differences found on entry did not influence the results. Timolol reduced mortality by 39% (Fig. 3), sudden death by 45%, and nonfatal reinfarction by 28%. Enough patients were included to make an analysis of adverse effects meaningful. Adverse effects were more common in the timolol group, but they may be considered minor in view of the reduction of mortality. The clinical need to treat patients with a beta blocker was the major reason for withdrawal from the study.

The effect of metoprolol on the 3-month mortality rate was examined in a double-blind stratified randomized trial in patients with definite or suspected acute MI in Göteborg, Sweden.[13] Treatment with metoprolol or placebo was started as soon as possible after the patient's arrival in the hospital and was continued for 3 months. Metoprolol was given as a 15-mg intravenous dose followed by oral administration of 100 mg twice daily. The trial included 1,395 patients who were allocated to various risk groups; within each group, patients were randomly assigned to treatment with metoprolol or placebo. Sixty-two patients in the placebo group (8.9%) and 40 in the metoprolol group (5.7%) died ($p < 0.03$). Mortality was reduced by 36% (Fig. 4). This study was the first to show a beneficial effect on short-term mortality rate after early initiation of treatment.

The Beta-Blocker Heart Attack Trial (BHAT),[14] sponsored by the National Heart, Lung, and Blood Institute, was a randomized, double-blind, multicenter trial of propranolol versus placebo in 3,837 patients. The study showed a 26% reduction of total mortality (Fig. 5). The design comprised a dose titration from 120 to 240 mg/day. The cumulative placebo mortality is low after 30 months of follow-up. The study was closed prematurely on advice from the Policy and Data Mon itoring Board.

The corroborative evidence of propranolol after M is also shown in another trial.[15] This study was pro spective, randomized and double-blind in a high-ris group of MI patients. Altogether, 560 patients entere the trial and were treated with 40 mg of propranolol times daily or with placebo. After 1 year, sudden death were reduced in the propranolol-treated group (Fig. 6) but total mortality or nonfatal reinfarctions were not

Conclusions

Several positive prospective studies strongly suppor the concept that chronic beta blockade of patient during the postinfarction period effectively reduce mortality. The question remains whether the short-terr mortality during the hospital period can be also be re duced. Only 2 early-entry studies have shown a decreas of long-term mortality.[11,13]

The findings in the studies with alprenolol, practolo timolol, metoprolol, and propranolol are probably no due to chance. How different beta blockers reduc mortality is not known, and one must be cautious i ascribing this secondary preventive effect to all bet blockers. In the next 6 months, several secondary pre ventive trials using other beta blockers may answer thi question. The available beta blockers vary in $beta_1$ an $beta_2$ affinity, intrinsic sympathomimetic activity an membrane stabilization activity. There is evidence t suggest that 1 ancillary property of beta blockers i clinically more useful than another. The only charac teristic common to all beta blockers with a positive ef fect on survival is $beta_1$-receptor blockade.

It is difficult to refrain from giving postinfarctio patients alprenolol, timolol, metoprolol or propranolc as long-term standard treatment. In Göteborg, long term administration of beta blockers has been use routinely after MI since 1975. Ideally, treatment shoul be reserved only for patients likely to derive benefi

from the treatment. Since some 60% of postinfarction patients have traditional indications for beta blockers, such as hypertension or angina pectoris, the problem of selecting patients for secondary prophylaxis is diminished. Mortality can be better predicted than reinfarction, but several studies have also shown a decreased reinfarction rate (Table II), suggesting that all patients should be treated.

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The Effect of High-Dose Intravenous Nitroglycerin on Cardiovascular Hemodynamic Features and Left Ventricular Function at Rest and During Exercise in Patients With Exertional Angina

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Intravascular pressures, cardiac output and left ventricular function were measured at rest and during exercise in 14 patients with stable angina pectoris before and during an intravenous nitroglycerin infusion. Nitroglycerin was infused at a rate sufficient to reduce mean arterial pressure at rest by 15 to 25 mm Hg.

At rest, the end-diastolic volume index decreased from 57 ± 13 to 39 ± 3 ml/m^2, stroke volume index from 32 ± 6 to 24 ± 5 ml/m^2 and mean arterial pressure from 112 ± 16 to 91 ± 14 mm Hg. The cardiac output was maintained by an increase in heart rate from 73 ± 9 to 92 ± 37 beats/min. The left ventricular ejection fraction increased from 57 ± 7 to 62 ± 9% because the stroke volume decreased less than the end-diastolic volume.

All 14 patients were limited by angina in the prenitroglycerin exercise study, and the mean ST-segment depression at maximal work load was 2.2 ± 1.2 mm. At identical work loads in the nitroglycerin study, only 4 patients had angina, and the mean ST-segment depression was 0.3 ± 0.5 mm. Ten of the 14 patients improved their exercise performance by at least 30 W.

Comparing the 2 exercise studies at the maximal work load achieved in the prenitroglycerin study, the mean pulmonary artery wedge pressure was decreased from 23 ± 6 to 6 ± 4 mm Hg, the end-diastolic volume index from 38 ± 15 to 27 ± 12 ml/m^2 and the mean arterial pressure from 132 ± 8 to 114 ± 13 mm Hg. The stroke volume index and the heart rate were not significantly altered and the ejection fraction increased from 56 ± 8% to 66 ± 8%.

Thus, in the high dose administered, nitroglycerin decreased left ventricular filling pressure, heart size and stroke volume at rest and increased the ejection fraction. During exercise, nitroglycerin decreased myocardial ischemia and improved exercise tolerance. An increase in exercise ejection fraction was associated with an increase in the ratio of systolic pressure to end-systolic volume, suggesting that there was an improvement in contractile performance.

With the resurgence of interest in antianginal drugs, nitroglycerin has become the standard with which new drugs are compared. However, the hemodynamic effects of nitroglycerin are complex and still not completely understood,[1] although it is generally accepted that they are important in reducing myocardial ischemia.[2]

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Early studies demonstrated that nitroglycerin is a potent dilator of capacitance vessels,[3] causing a marked reduction in ventricular preload.[4,5] Recent studies using radionuclide ventriculography have described the effect of nitroglycerin on cardiac volume at rest and during exercise. Sorensen et al[6] reported that in normal subjects during exercise, nitroglycerin decreases end diastolic volume with no change in ejection fraction. Slutsky et al[7] and Borer et al[8] demonstrated that in patients with coronary artery disease, nitroglycerin increases the ejection fraction during exercise.

In this study, hemodynamics and left ventricular (LV) function were measured simultaneously at rest and during exercise, before and after intravenous nitro

glycerin, in patients with ischemic heart disease to further delineate its effects on cardiac work load and performance.

Methods

Patients: Fourteen men with a typical history of stable effort angina of >3 months' duration and a positive exercise test result associated with angina were studied. Three patients had had a previous myocardial infarction and 11 had significant coronary disease demonstrated by coronary angiography. All medications were stopped for 1 week before the study, except short-acting nitrates, which were omitted for 12 hours.

On the morning of the study, a radial artery cannula and a No. 7Fr Swan-Ganz thermodilution catheter were inserted percutaneously. Simultaneous hemodynamic and radionuclide measurements were made at rest and during exercise with the patient positioned semisupine 45° to the horizontal on an exercise table attached to an electronically braked bicycle ergometer. The zero reference point for pressures was set at the fourth intercostal space in the midaxillary line.

The exercise work load was increased by 15 W every 3 minutes. Patients were asked to exercise until prevented by symptoms from continuing. When angina was the limiting symptom, they were asked to continue exercising until they had angina of at least moderate severity compared with their usual exertional episodes.

During exercise, heart rate, electrocardiographic lead CM5, radial artery pressure and pulmonary artery pressure were recorded continuously. A 12-lead electrocardiogram was recorded every minute. Cardiac output was measured by thermodilution using an Instrumentation Laboratory computer (model 701) and ice-cold 5% dextrose solution. Five cardiac output measurements were made at rest. During exercise, at least 3 cardiac output measurements were made in the last 1.5 minutes of each 3-minute exercise level.

Simultaneous radial and pulmonary artery blood samples were collected at rest and at the end of each exercise level for measurement of oxygen saturation. The radial artery sample was also used for measuring hemoglobin at rest and during exercise. The arteriovenous oxygen content difference was calculated as 1.39 × the difference between radial artery and pulmonary artery oxygen saturations × hemoglobin level. Oxygen consumption was calculated as the cardiac output × arteriovenous oxygen difference.

Radionuclide ventriculography: Multiple-gated equilibrium radionuclide ventriculography was performed after in vivo labeling of red cells with technetium-99m.[9] Imaging was performed in a modified left anterior oblique position by an Ohio nuclear gamma camera (Sigma 420) equipped with a 30° slant-hole, high-sensitivity collimator, and interfaced to a PDP-11 computer. Counts were collected for 6 minutes at rest with simultaneous recordings of intravascular pressures and cardiac output. During exercise, counts were collected in the last 2 minutes of each 3-minute stage. The composite cardiac cycle was divided into 24 frames for analysis by a variable region of interest. LV ejection fraction was calculated from the background-corrected time-activity curve.[10] Stroke volume was calculated from the thermodilution cardiac output normalized for body surface area and expressed as the stroke volume index. End-diastolic volume index was calculated by dividing the thermodilution stroke volume index by the radionuclide ejection fraction. End-systolic volume index was calculated as end-diastolic volume index minus the stroke volume index.

A control rest and exercise study was performed 1 hour after insertion of the catheters. Patients were then allowed to recover from the control exercise for 2 hours before an intravenous infusion of nitroglycerin was started. Nitroglycerin was administered as a 500 μg/ml solution using a microdrip burette with polyvinyl tubing and a volumetric infusion pump (IMED 922). This report describes the effect of administering a high

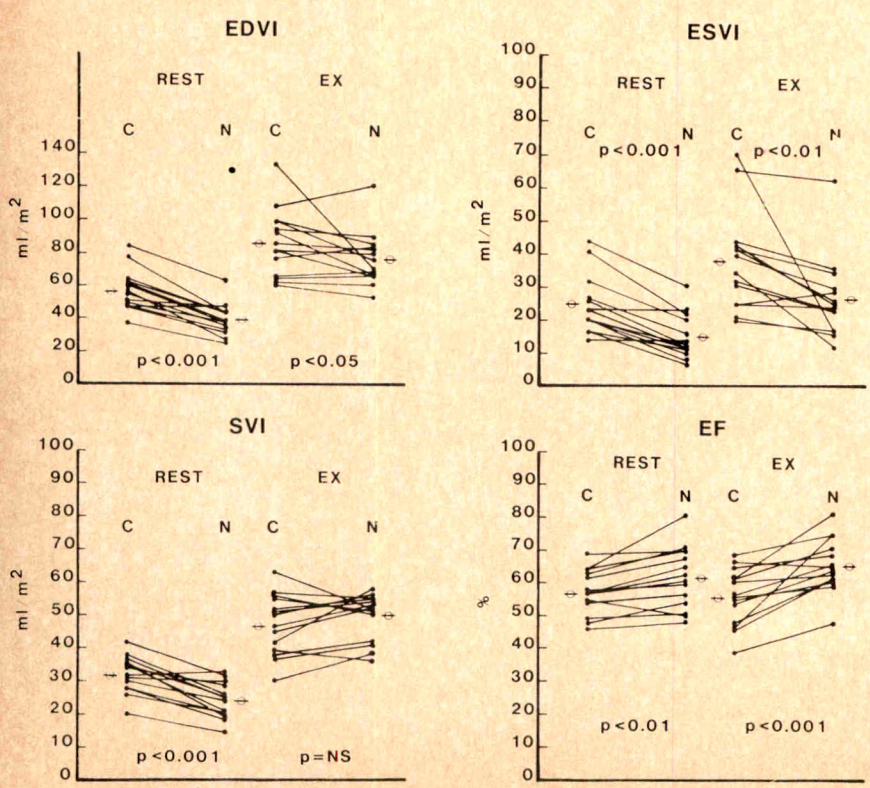

FIGURE 1. End-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI) and ejection fraction (EF) in control (C) and nitroglycerin (N) studies at rest and during exercise (EX). The exercise studies were compared at identical work loads for each patient. p = probability; NS = not significant.

dose of nitroglycerin. The infusion rate was started at 0.17 ml (83 μg)/min and increased by 0.17 ml/min every 5 minutes until the mean arterial blood pressure decreased by 15 to 25 mm Hg. When this end point had been reached, the infusion was maintained at a constant rate. After a further 15 minutes of observation to ensure a steady state, repeated rest and exercise observations were performed during the nitroglycerin infusion. The final infusion rates ranged from 0.17 ml (83 μg)/min to 0.75 ml (375 μg)/min (mean 0.42 ml[208 μg]/min). Allowing for the rate of adsorption to plastic tubing measured in our laboratory, the dose actually received by the patient probably ranged from 0.52 to 3.57 μg/kg/min (mean 1.28).

Unless otherwise stated, results are expressed as mean ± standard deviation. Hemodynamic features and LV function at rest and exercise during the nitroglycerin infusion were compared with results during the control rest and exercise study using a 3-way analysis of variance, unless significant interaction was detected, in which case control and nitroglycerin studies were compared at rest and during exercise using a paired *t* test.

Results

Rest: The effect of nitroglycerin on LV volume and function are shown in Figure 1. At rest, the end-diastolic volume index decreased from 57 ± 13 to 39 ± 13 ml/m^2 and end-systolic volume index decreased from 24 ± 17 to 15 ± 7 ml/m^2. Because end-diastolic volume decreased to a greater extent than end-systolic volume, the stroke index decreased from 32 ± 6 to 24 ± 5 ml/m^2. The resting LV ejection fraction increased from 57 ± 7 to 62 ± 9%.

Mean arterial pressure was reduced by the nitroglycerin infusion from 112 ± 16 to 91 ± 14 mm Hg and systemic vascular resistance was reduced from 2,082 ± 471 to 1,805 ± 372 dynes s cm^{-5} (Fig. 2). Mean pulmonary artery wedge pressure decreased from 3 ± 2 to 1 ± 2 mm Hg.

Heart rate increased from 73 ± 9 to 92 ± 27 beats/min (Fig. 3). This increase in heart rate compensated for the decrease in stroke volume, and there was no significant reduction in cardiac index. The increase in heart rate was also accompanied by an increase in the ratio of the peak systolic pressure to end-systolic volume index (systolic pressure volume ratio) from 7.4 ± 2.8 to 10.1 ± 5.1 (Fig. 3).

Exercise: All patients stopped with angina in the control study. The mean ST-segment depression at the maximal work load was 2.2 ± 1.2 mm. The mean oxygen consumption was 15.9 ± 5.3 ml/kg, compared with 3.5 ± 0.3 ml/kg at rest. At the same work load for each patient during the nitroglycerin infusion, only 4 of the 11 patients had angina, which was milder than in the control study, and the mean ST-segment depression was 0.3 ± 0.5 mm.

End-diastolic and end-systolic volume increased significantly above resting levels during both exercise studies (Fig. 1). When compared at the maximal work load achieved during the control study, the end-diastolic volume index and the end-systolic volume index were lower during the nitroglycerin study than during the control study. The reduction in end-systolic volume index, from 38 ± 15 to 27 ± 12 ml/m^2, was similar to the reduction in end-diastolic volume index, from 86 ± 21 to 76 ± 16 ml/m^2; the stroke index was the same during control (47 ± 9 ml/m^2) and nitroglycerin (49 ± 7 ml/m^2) exercise. However, the ejection fraction was higher

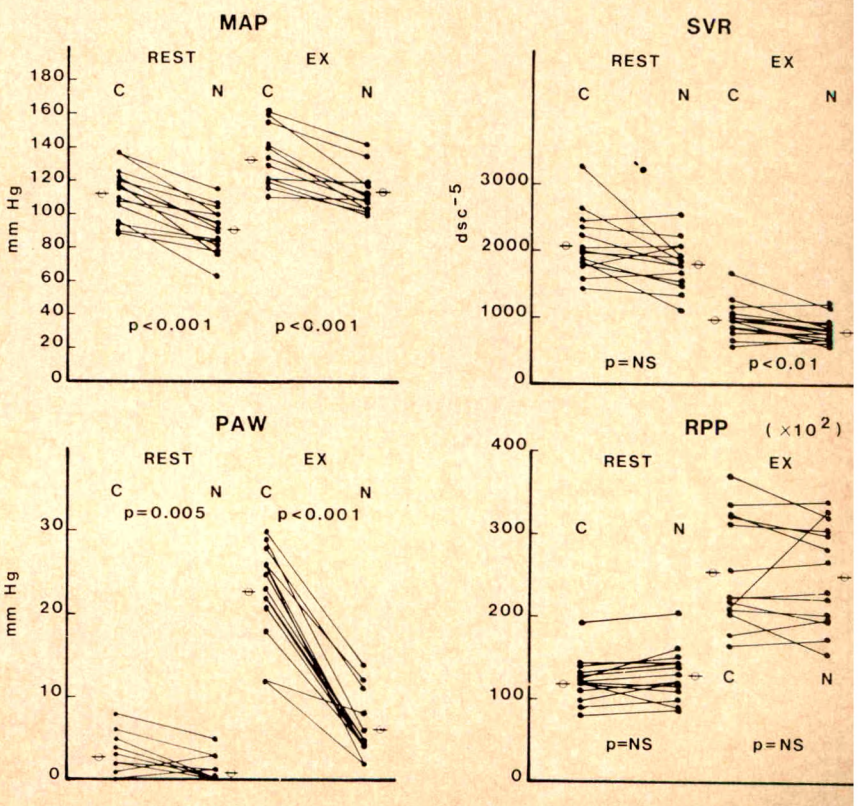

FIGURE 2. Mean arterial pressure (MAP), systemic vascular resistance (SVR), pulmonary artery wedge pressure (PAW) and rate-pressure product (RPP) in control (C) and nitroglycerin (N) studies at rest and during exercise (EX). The exercise studies were compared at identical work loads for each patient. p = probability; NS = not significant.

during the nitroglycerin exercise (66 ± 8 versus 56 ± 8%). The mean pulmonary artery wedge pressure increased dramatically during exercise, to 23 ± 6 mm Hg. This increase was attenuated during the nitroglycerin infusion, and at the same work load it was only 6 ± 4 mm Hg (Fig. 2).

The vasodilator effect of nitroglycerin was maintained during exercise and the mean arterial pressure at identical work loads was 132 ± 8 mm Hg in the control study, compared with 114 ± 13 mm Hg in the nitroglycerin study (Fig. 2). Heart rate was slightly higher during the nitroglycerin study compared with control, but the difference was not significant (Fig. 3). The rate-pressure product (heart rate × systolic arterial pressure × 10^{-2}) did not differ significantly: At identical work loads it was 254 ± 66 in the control study and 251 ± 30 in the nitroglycerin study (Fig. 2). Although systemic vascular resistance decreased from rest during both exercise studies, it remained lower during the nitroglycerin study (Fig. 2).

At identical work loads, there was no significant difference in arteriovenous oxygen difference (Fig. 3). However, the cardiac index was slightly higher in the nitroglycerin study (6.0 ± 1.2 versus 5.5 ± 1.2); the systolic pressure-volume ratio was significantly higher in the nitroglycerin study (9.1 ± 4.1 versus 6.6 ± 3.3) (Fig. 3).

The reduction in myocardial ischemia produced by nitroglycerin at identical work loads was accompanied by a significant improvement in exercise performance. Thirteen of 14 patients improved their exercise tolerance by at least 1 exercise level (15 W) and 10 patients improved by at least 2 exercise levels (30 W). Oxygen consumption at peak exercise during the nitroglycerin study was 23.4 ± 6.6 ml/kg/min, an average increase of 7.5 ml/kg/min, or approximately 2.4 METS, over the control study. At peak exercise during the nitroglycerin study, there was 1.2 ± 1.2 mm of ST depression. Of the 13 patients who improved their exercise tolerance, 5 did not have angina during the nitroglycerin study and 3 had it only very mildly (compared with the control study), and it was not the limiting factor.

Hemodynamic values at the maximal work load in the control study and at the maximal work load in the nitroglycerin study are shown in Table I. In achieving the increased exercise performance, the end-diastolic volume index, pulmonary artery wedge pressure and mean arterial pressure remained below the levels reached during control exercise. In contrast, heart rate, cardiac index, arteriovenous oxygen difference and rate-pressure product increased to levels significantly higher than those achieved during the control exercise period. Although the ejection fraction remained significantly higher at peak exercise, during nitroglycerin the systolic pressure-volume ratio was not significantly different.

Discussion

The hemodynamic response to nitroglycerin is influenced by the broad range of individual sensitivities to the drug and by the variable effect that different dose levels have on venous, arterial and arteriolar smooth muscle.[1,2] In the present study, these factors were controlled by giving nitroglycerin intravenously at a rate

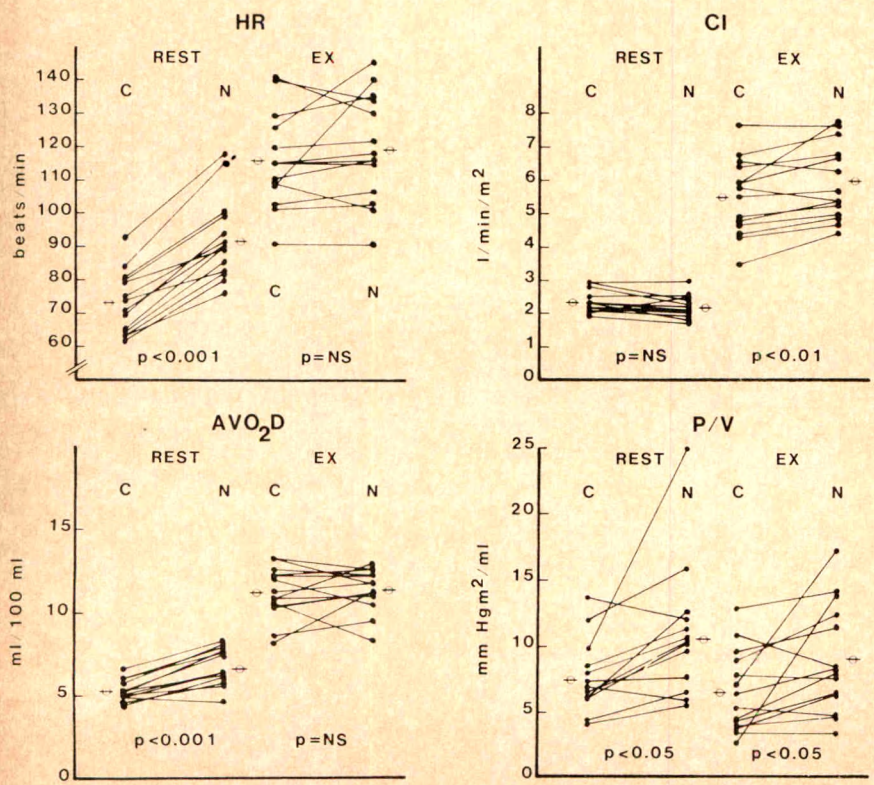

FIGURE 3. Heart rate (HR), cardiac index (CI), arteriovenous oxygen content difference (AVO_2D) and ratio of peak systolic pressure to left ventricular end-systolic volume index (P/V) in control (C) and nitroglycerin (N) studies at rest and during exercise (EX). The exercise studies were compared at identical work loads for each patient. p = probability; NS = not significant.

TABLE I Hemodynamic Values and Left Ventricular Function at Maximal Work Load in Control and Nitroglycerin Exercise Studies

	Control	Nitroglycerin	p
EDVI (ml/m^2)	86 ± 20	79 ± 28	<0.05
ESVI (ml/m^2)	38 ± 15	36 ± 4	NS
SVI (ml/m^2)	47 ± 9	52 ± 8	<0.05
EF (%)	56 ± 8	63 ± 8	<0.01
P/V ratio	6.6 ± 3.1	7.6 ± 3	NS
PAWP (mm Hg)	23 ± 6	9 ± 4	<0.001
MAP (mm Hg)	132 ± 18	116 ± 13	<0.001
RPP ($\times 10^{-2}$)	254 ± 66	290 ± 59	<0.01
SVR (dyne s cm^{-5})	993 ± 277	699 ± 162	<0.001
HR (beats/min)	116 ± 14	136 ± 13	<0.001
CI (liters/min/m^2)	5.5 ± 1.2	7.1 ± 1.3	<0.001
AVO_2D	11.2 ± 1.6	13 ± 1.3	<0.05

AVO_2D = arteriovenous oxygen content difference; CI = cardiac index; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; HR = heart rate; MAP = mean arterial pressure; PAWP = pulmonary artery wedge pressure; P/V ratio = peak systolic pressure to end-systolic left ventricular volume ratio; RPP = heart rate × systolic arterial pressure; SVI = stroke volume index; SVR = systolic vascular resistance.

sufficient to produce a similar reduction in LV filling pressure and arterial pressure in all patients.

Nitroglycerin usually causes a decrease in stroke volume at rest secondary to the venodilation and reduction in LV filling pressures.[6,11,12] Occasionally, there may be a profound decrease in cardiac output with bradycardia.[13] In the present study, the decrease in stroke volume was compensated by a reflex increase in heart rate, and cardiac output was maintained. However, there was a decrease in blood pressure and a decrease in systemic vascular resistance, indicating that at the dose rates administered, nitroglycerin dilated arterioles as well as veins.

This study reconciles the reduction in stroke volume at rest caused by nitroglycerin with the reported increase in ejection fraction reported in radionuclide[7,8] and echocardiography[5] studies. Stroke volume decreased less than the end-diastolic volume and the ratio of the 2, the ejection fraction, increased.

This study was designed so that all patients would have angina and ST-segment depression during the control exercise study. The mean work level achieved during the control study was only 5 METS. Although this was an open study, there is reasonable evidence that intravenous nitroglycerin significantly reduced myocardial ischemia during exercise. At identical exercise levels, there was a marked reduction in ST-segment depression; whereas all patients were limited by moderate to severe angina during the control study, at the same work level in the nitroglycerin study, only 4 patients had angina, and it was very mild. The best evidence that nitroglycerin decreased myocardial ischemia was the improvement in exercise performance by an average of 3 METS during the nitroglycerin study. All 13 patients who improved their exercise performance achieved higher heart rates, rate-pressure products, cardiac outputs and ejection fractions compared with the control study.

The large increase in end-diastolic volume during the control exercise study is the usual finding in our laboratory, when patients with stable exertional angina exercise in a semisupine position.[14] This study has demonstrated that the increase in end-diastolic volume was associated with a similar increase in LV filling pressure to levels that would cause significant dyspnea in normal subjects.

It is likely that the LV filling pressures were actually higher than the recorded levels. At rest, the right atrial, pulmonary artery and pulmonary artery wedge pressures were lower than expected. We realized early in the study that the transducers were probably being set several centimeters too high for patients in a semisupine position, thus decreasing the recorded right-sided pressures. However, in the interest of consistency, we set the transducers at the same high level throughout the study.

End-systolic volume decreases when normal persons exercise.[6,7] The increase in end-systolic volume in this and other studies[7,15] when patients with coronary artery disease exercise is 1 of the major manifestations of LV ischemia and it is the mechanism underlying the increase in end-diastolic volume and filling pressures and the flat or decreasing ejection fraction response.

Nitroglycerin markedly reduced the LV filling pressure during exercise and maintained the systemic vascular resistance lower than during the control study. Despite the large decrease in filling pressures during exercise, the effect of nitroglycerin on cardiac volumes during exercise was less than that at rest. Although the reduction in volume was small, it is likely that wall tension, a major determinant of oxygen requirement, was significantly reduced by the lower filling pressure (Fig. 4).

Although nitroglycerin decreased stroke volume at rest, there was no consistent change during exercise and

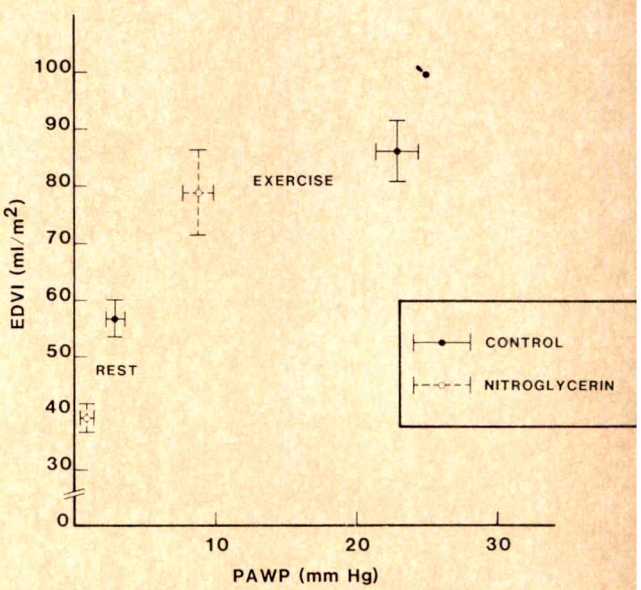

FIGURE 4. Relationship between end-diastolic volume index (EDVI) and pulmonary artery wedge pressure (PAWP) at rest and during exercise at identical work loads. Group mean and standard errors are shown for control studies and after nitroglycerin.

cardiac output tended to be higher during the nitroglycerin study. Thus, unlike beta blockers, which impede cardiac output, nitroglycerin enhances the delivery of oxygen to the exercising muscles. Presumably, the improvement in cardiac output during exercise was related to the absence of ischemic depression of cardiac output.

This study cannot answer the question of whether nitroglycerin improves pump function by a primary increase in myocardial oxygen supply. However, it does provide some evidence as to whether the improved cardiac performance is due to decreased external load alone, with persistent impairment of LV function, or whether there is a real improvement in contractile performance.

The LV ejection fraction is an index of contractile performance, and it was increased during the nitroglycerin study. However, the LV ejection fraction is sensitive to changes in afterload, and there is no doubt that the reduced LV volume and the reduced arterial pressure contributed to a significant reduction in afterload.

The ratio between the peak systolic pressure and the end-systolic volume has recently been explored as an index of the contractile state which takes into account the afterload.[15–17] In this study, nitroglycerin increased the pressure-volume ratio at rest and during exercise. The increase at rest may be due to an increase in contractility secondary to reflex changes stimulated by the reduction in blood pressure.

In both control and nitroglycerin studies, the pressure-volume ratio was lower during exercise than at rest, indicating that at this work level the contractile state of the heart was impaired by ischemia, compared with resting state. Despite this decrease from resting levels, the pressure-volume ratio during nitroglycerin exercise was higher than that during the control study, indicating that the reduction in myocardial ischemia during nitroglycerin exercise was associated with improved contractile performance. As patients exercised to peak work load during the nitroglycerin infusion, the ratio decreased to a level similar to that at maximal exercise in the control study.

In summary, intravenous nitroglycerin was given at a dose which produced both venous and arterial dilatation. At rest, the reduction in preload caused a decrease in stroke volume, but the cardiac output was maintained by an increase in heart rate. During exercise, nitroglycerin produced a significant decrease in myocardial ischemia. Its major effect on hemodynamics was to attenuate the large increase in filling pressure. In contrast to the findings at rest, the reduction in preload during exercise caused only a small decrease in cardiac volume and did not decrease stroke volume. LV ejection fraction was increased; this improvement in cardiac function was possibly due to an improvement in the contractile state because of reduced ischemia, rather than the effect of reduced load alone.

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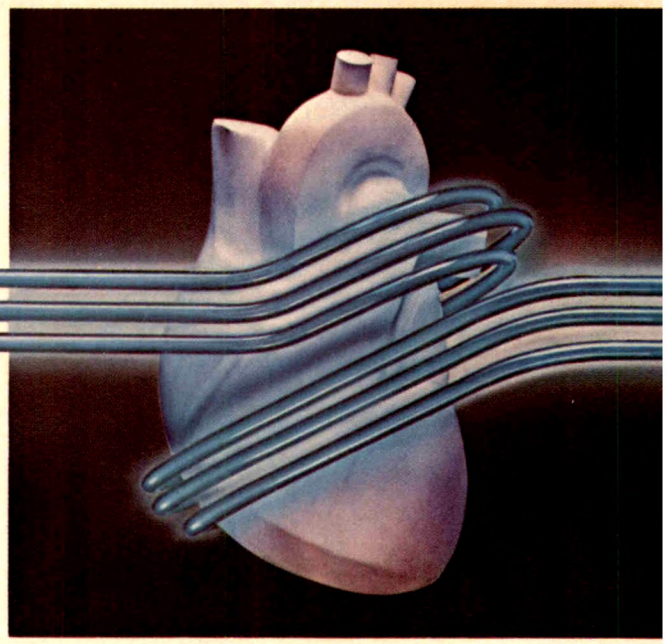

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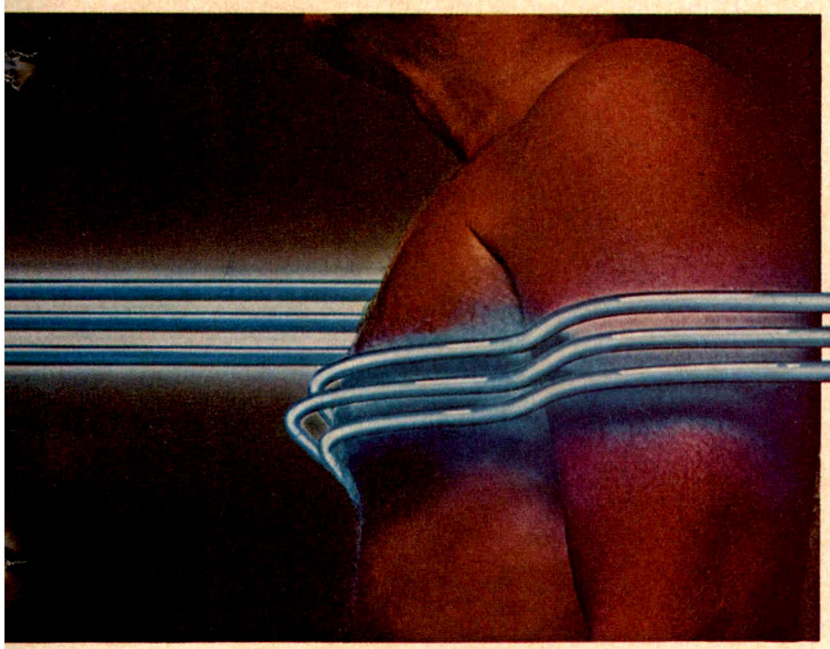

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Simplified core therapy begins with 80 mg once daily. Although individual patients may respond to various doses, the average optimal dose in angina pectoris is 160 mg once daily.

When converting patients from other beta blockers, including INDERAL tablets, switch to the nearest milligram equivalent of INDERAL LA once daily and evaluate clinical results to determine if dosage adjustment is necessary. For arrhythmias, use conventional INDERAL (propranolol HCl) tablets.

80 mg 120 mg 160 mg

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Please see next page for brief summary of prescribing information.

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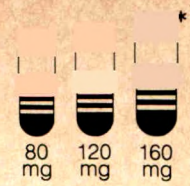

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)*
INDERAL® LA BRAND OF propranolol hydrochloride
(Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta-blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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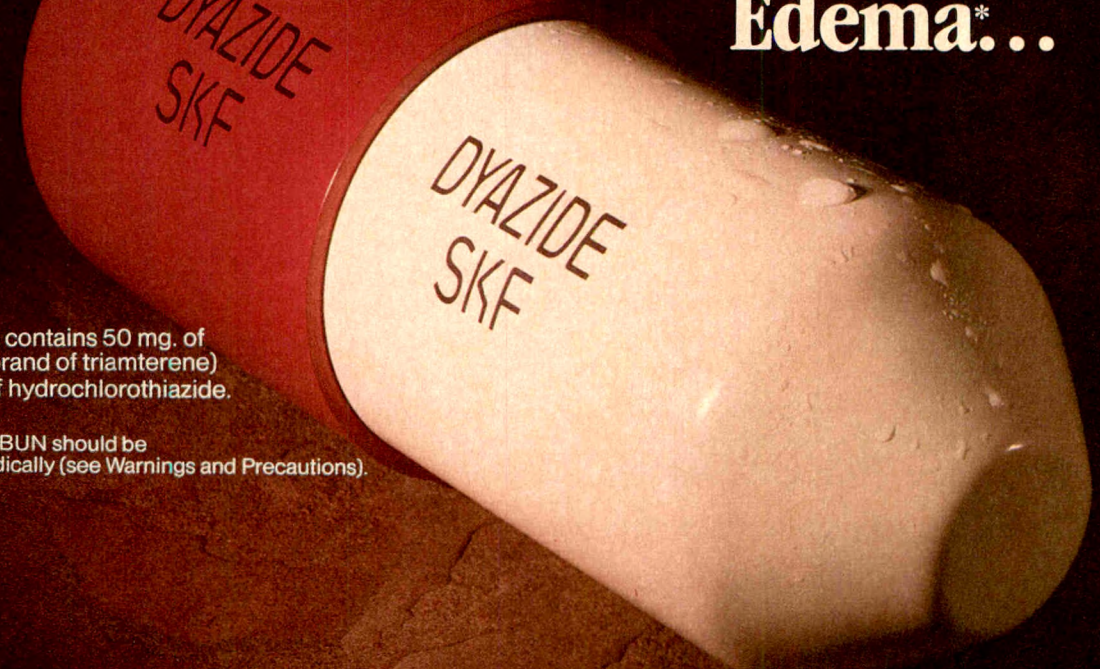

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* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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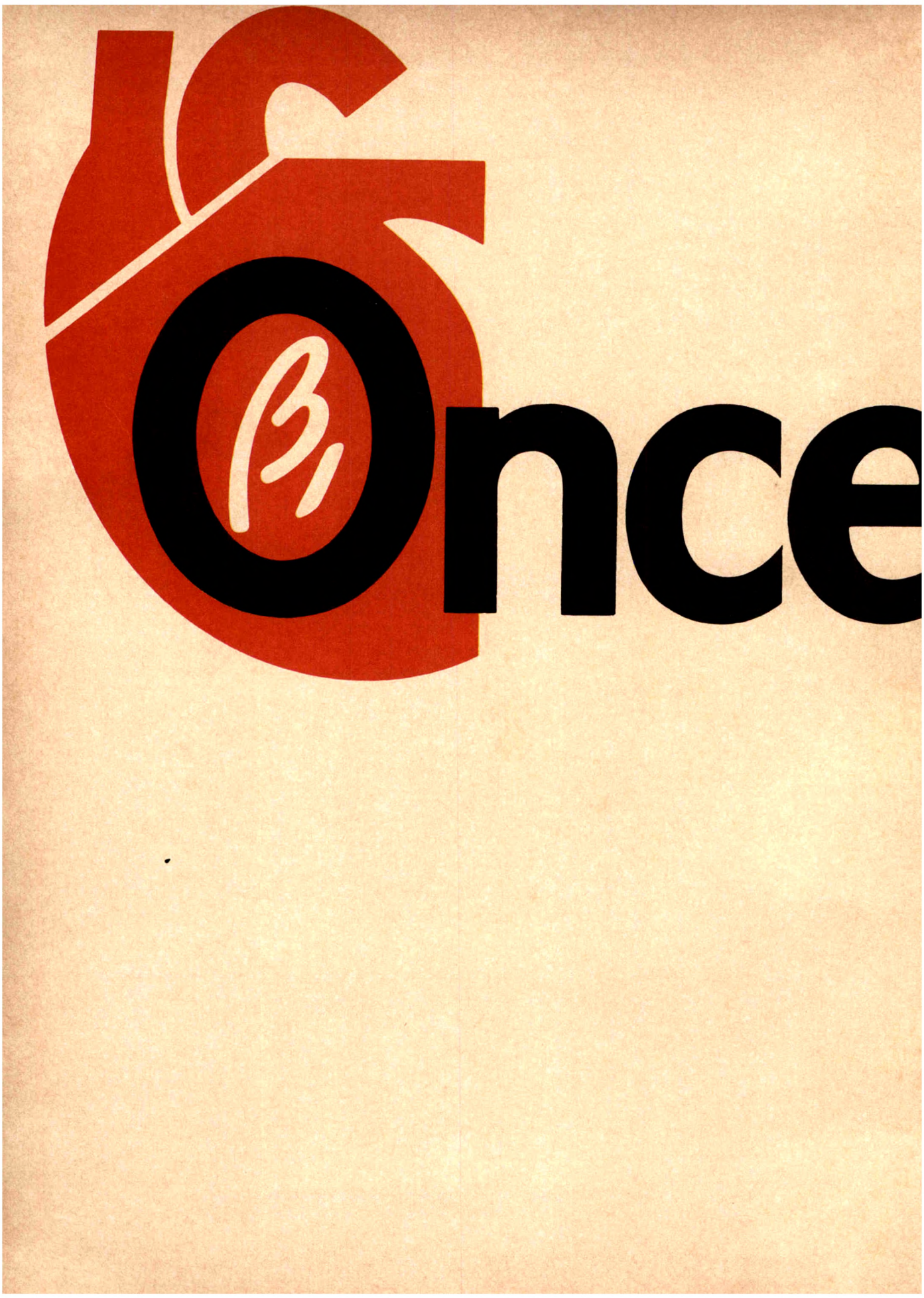
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Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. $Beta_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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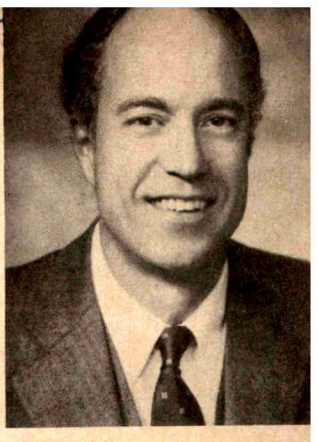

Mitral Commissurotomy—Still a Good Operation

Recently, I examined an operatively excised, severely stenotic mitral valve that was free of calcific deposits (by radiography of the excised valve) and of associated mitral regurgitation (by left ventricular angiography). The patient had no evidence of dysfunction of either the tricuspid or aortic valves. I asked the surgeon who had performed the mitral valve replacement (MVR) why that procedure was performed rather than mitral valve commissurotomy (MVC). I was surprised to hear that he "rarely did MVC anymore" and that he had "more confidence in MVR than in MVC." He had used a mechanical prosthesis for the MVR, which necessitated anticoagulant therapy for the rest of this 36-year-old woman's life. When I mentioned that chronic anticoagulant therapy would not have been necessary had MVC been performed, he responded that "MVR was still worth the difference." I disagree, and so does Bonchek[1] in the editorial in this issue.

In 1978, Lachman and I[2] radiographed 164 operatively excised stenotic mitral valves and quantitated the amount of calcific deposits in them. Of the 164 valves, 14 had absent and 43 minimal calcific deposits on x-ray examination of the excised valve. Of the 57 patients with absent or minimal calcific deposits, 37 had moderate to severe mitral regurgitation, and therefore, each clearly warranted MVR. The remaining 20 had absent or minimal calcific deposits and absent or minimal mitral regurgitation as determined by left ventricular angiography; nevertheless, MVR had been performed. We analyzed retrospectively those 20 patients to examine if MVR was preferable to MVC.[3]

To answer this question unequivocally, the stenotic mitral valves in patients who had only commissurotomy would have to be studied morphologically and radiographically in the same manner as those that were excised and replaced. Obviously, the nonexcised valve cannot be examined in the same manner as the excised valve. Nevertheless, the ideal valve for MVC in the past has bee considered to be the stenotic one that is free of calcif deposits, free of significant mitral regurgitation, and mobil The excised mitral valves in the 20 patients whom w analyzed were free of calcific deposits by preoperati examination (or nearly so by radiography of the excise valve, a far more sensitive technique than x-ray or flu roscopy through the chest wall), and none had significa regurgitation by left ventricular angiography. The degre of mobility was infrequently described in the operati note. All 20 patients analyzed would probably have bee acceptable candidates for MVC in the pre–valve r placement era. Why, then, might valve replacement b performed with its prosthetic- or bioprosthetic-relat complications rather than MVC in this circumstance?

Of the 20 patients studied by Lachman and me,[3] seve reasons appeared to account for MVR rather than MV (1) *Another cardiac valve was also replaced* (13 patient Therefore, if the patient is required to have anticoagula therapy for a prosthesis in the tricuspid or aortic val position, MVR may be the more reasonable procedure a will avoid the risk of significant regurgitation or incomple relief of the stenosis by MVC. (2) *Cardiopulmonary bypa was used* (all 20 patients). This procedure obviously allo visual inspection of the valve, something not possible wh MVC is done as a "closed" procedure. I suspect that t visually inspected stenotic mitral valve is more frighteni to the observer than is the palpated stenotic valve. Th visual inspection alone, particularly when valve replac ment is a reasonable and uncriticized option, may push t surgeon toward replacement rather than simple co missurotomy in some patients. (3) *Some surgeons h relatively little experience with MVC* (17 patients). Of t 20 patients we analyzed, 17 were operated on by surgec <40 years old when the operation was done. As point out by Bonchek,[1] younger surgeons have had much le

Continued on page A10

experience with MVC than with MVR. (4) *Dissatisfaction with attempted MVC* (3 patients). (5) *Previous MVC had been performed* (11 patients). Although there is disagreement on this point, a mitral valve that has had a commissurotomy and later becomes severely stenotic can nevertheless have another MVC as long as calcific deposits are absent and regurgitation is absent or minimal. (6) *Incorrect identification of mitral calcific deposits* (2 patients). A calcific deposit was described in the mitral leaflets at operation, but x-ray of the excised valve showed that it was devoid of calcium.

Each of these 6 factors contributed in ≥ 1 of the 20 patients analyzed to the final operative decision of MVC rather than MVR. Even though MVC has been performed for >30 years, the mere alternative of MVR appears to have somewhat altered the definition of the mitral valve previously considered ideal for MVC. We need to return to the earlier definition of the ideal mitral valve suitable for MVC.

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William C. Roberts, MD
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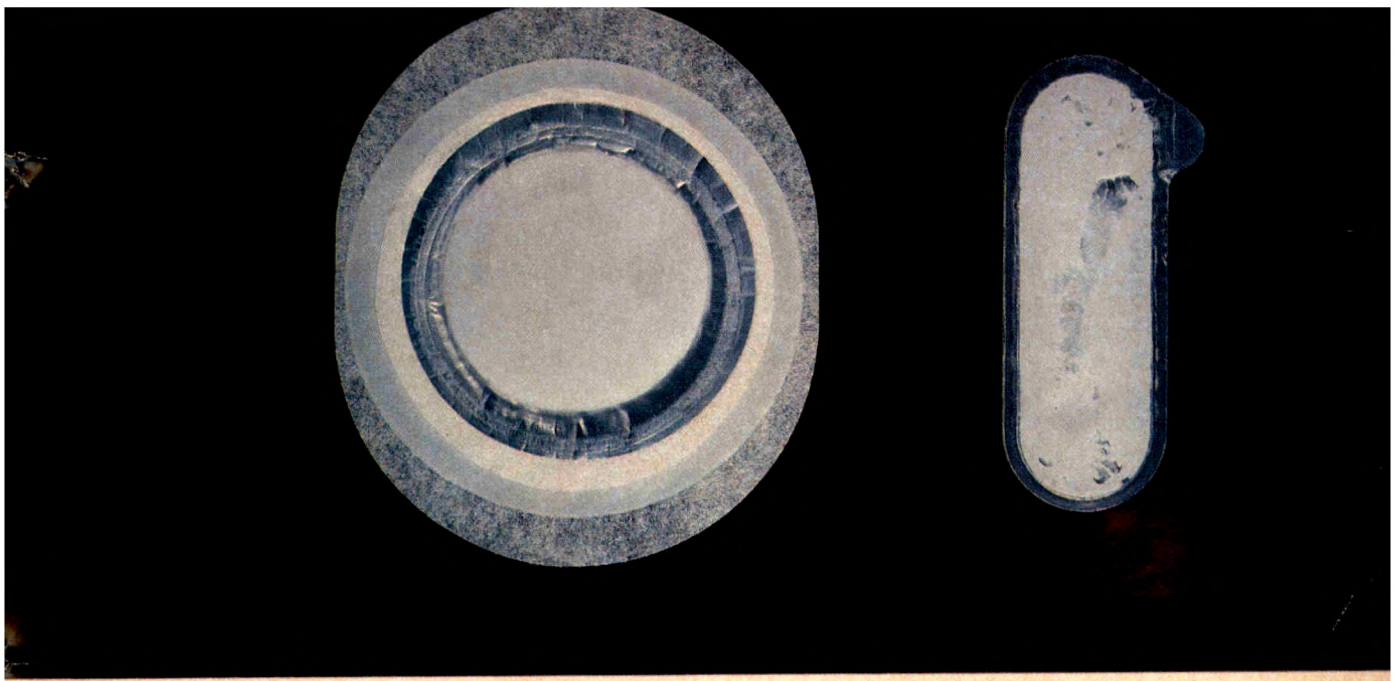

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DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release in vivo of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[2] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without a prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

References
1. Pharmacy acquisition cost (AWP), *Drug Topics Red Book*, 1982 (assuming a 50% markup).
2. Data on file: Key Pharmaceuticals, Inc. 01/83

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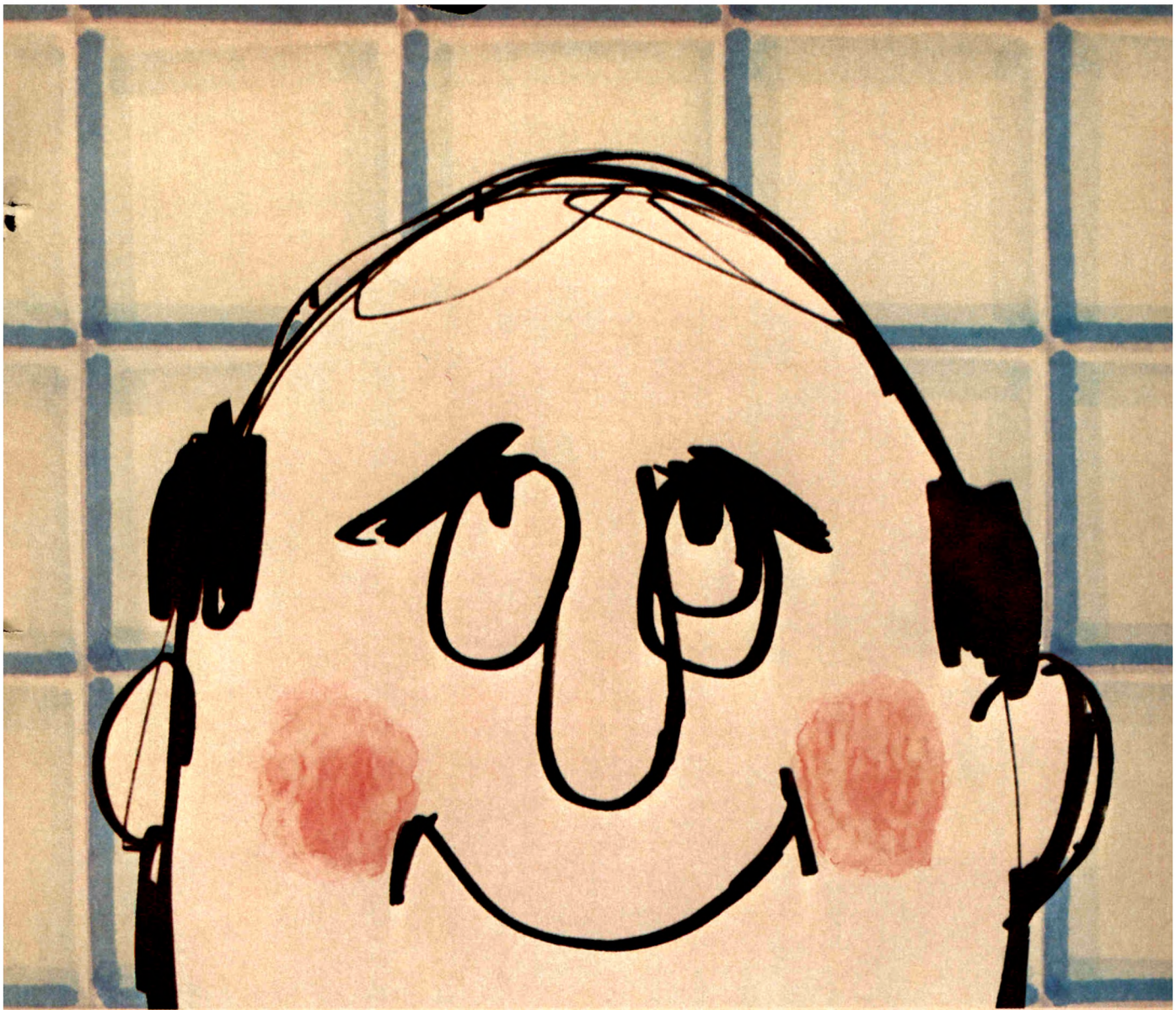

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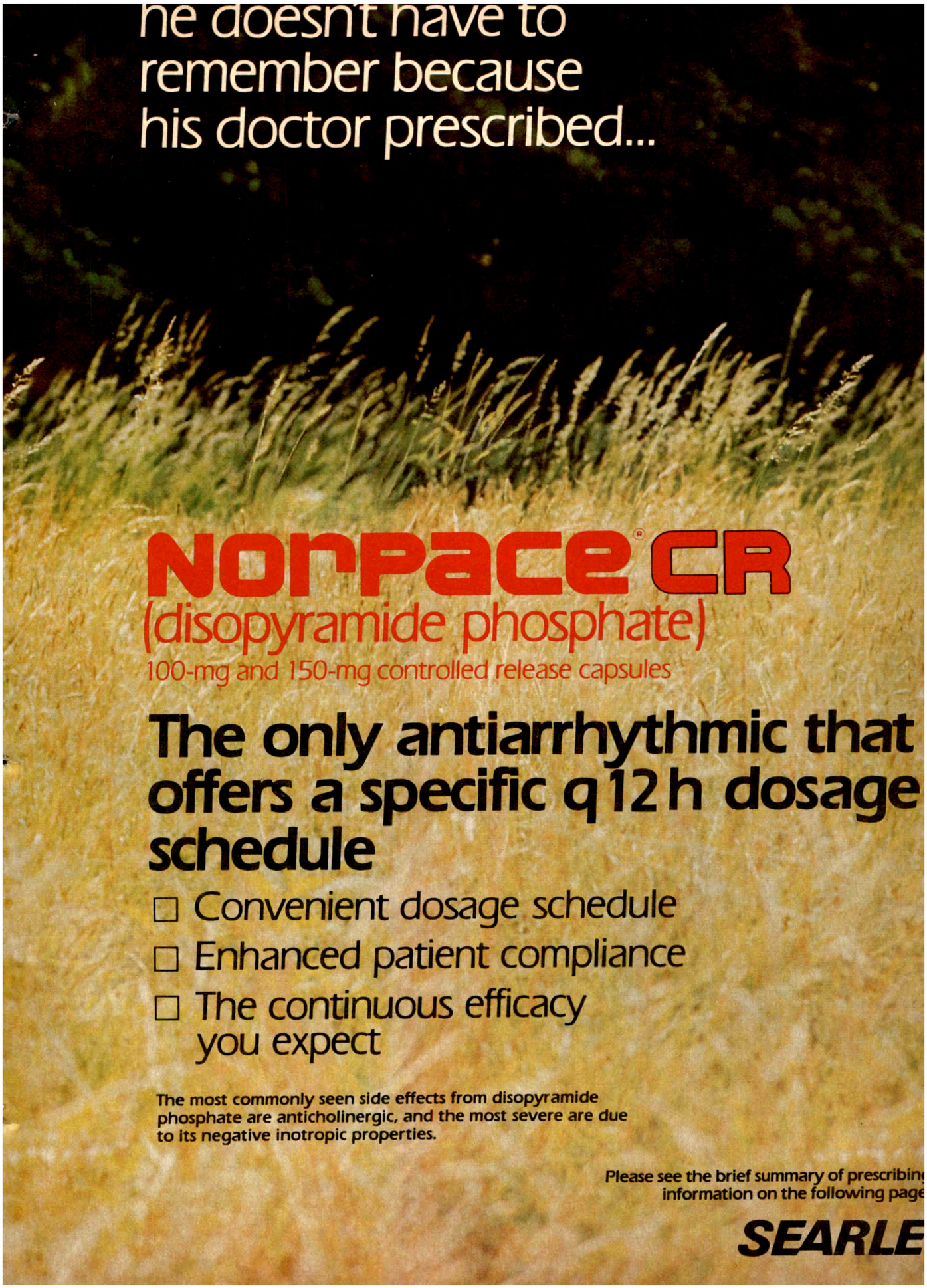
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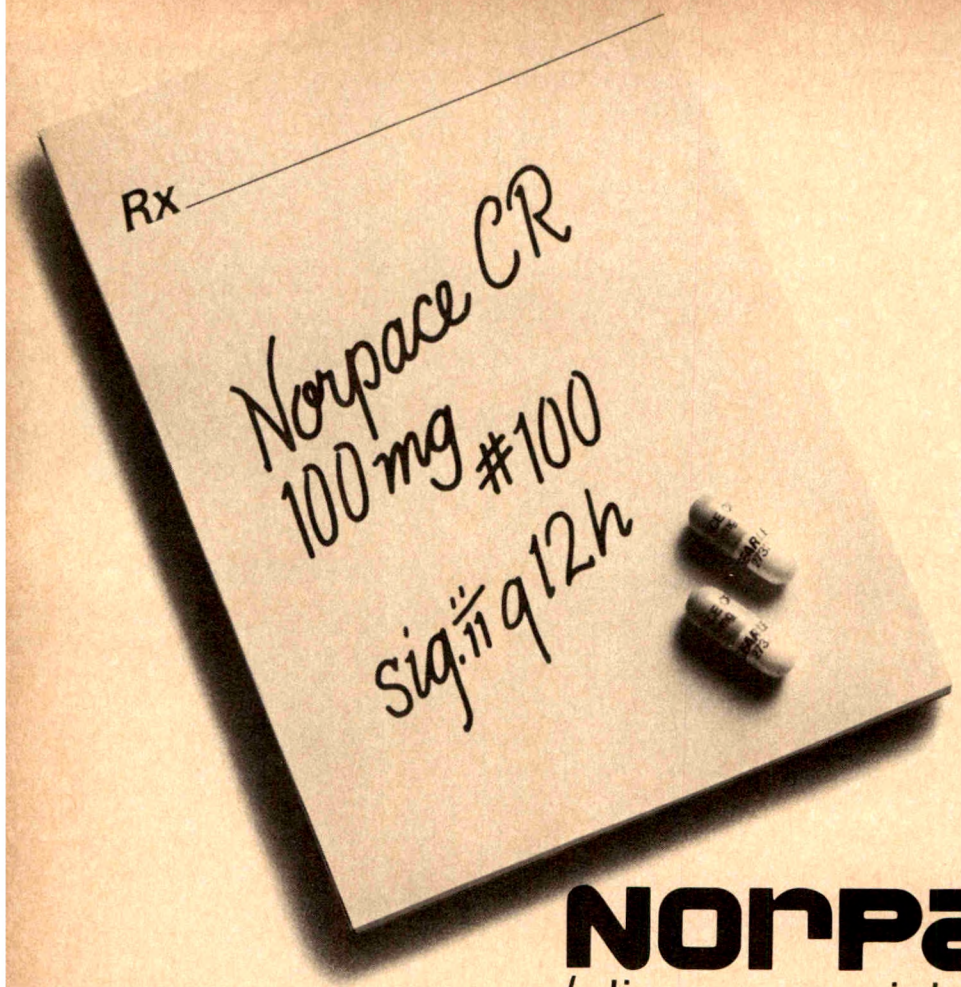

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Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. 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Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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CORONARY HEART DISEASE

221 Coronary Reperfusion and Bezold-Jarisch Reflex (Bradycardia and Hypotension)

PAOLO ESENTE, ALESSANDRO GIAMBARTOLOMEI, GOFFREDO G. GENSINI, and CARLOS DATOR

The occurrence of the Bezold-Jarisch reflex, a cardioinhibitory reflex characterized by bradycardia and hypotension, was observed in 20 of 92 patients undergoing intracoronary thrombolysis in a very early phase of acute myocardial infarction. Right coronary artery recanalization was frequently (65%) followed by the Bezold-Jarisch reflex with a close temporal relation. In only 22% of patients with a nonoccluded or nonrecanalized right coronary artery did hypotension and bradycardia develop. In 1 instance only, the reflex was elicited by recanalization of the left anterior descending coronary artery. Postural changes, atropine, or temporary pacing was successfully used in all but 1 patient, who required additional therapy. Left ventricular function studies 1 to 12 weeks after recanalization failed to show a better recovery among patients in whom the Bezold-Jarisch reflex developed. A cardioinhibitory reflex is frequently induced by reperfusion of the inferoposterior left ventricular wall. However, it does not appear to be a reliable predictor of myocardial salvage.

225 Natural History of Patients With Single-Vessel Disease Suitable for Percutaneous Transluminal Coronary Angioplasty

MARK A. HLATKY, ROBERT M. CALIFF, YIHONG KONG, FRANK E. HARRELL, Jr., and ROBERT A. ROSATI

To permit comparison of percutaneous transluminal coronary angioplasty (PTCA) with conventional therapy, the clinical outcome of patients who presented before PTCA became available, but who would be suitable for PTCA if they presented today, was established. One hundred ten patients were judged suitable for PTCA after review of their coronary angiograms. Five years after catheterization, 97% of the medically treated patients were alive, and 85% had not had a myocardial infarction. Fifty-six patients eventually underwent coronary bypass surgery. Five years after surgery, 91% were alive and 87% had not had a myocardial infarction. Functional capacity and employment were well maintained during follow-up. There were no significant differences in outcome between patients treated medically and those treated surgically. These data indicate that patients with single-vessel disease suitable for PTCA have an excellent prognosis when revascularization is reserved for those whose symptoms were not controlled adequately by medical therapy.

230 Detrimental Effect of Propranolol in Patients With Coronary Arterial Spasm Countered by Combination With Diltiazem

PIERRE Y. TILMANT, JEAN M. LABLANCHE, FRANÇOIS A. THIEULEUX, BERNARD A. DUPUIS, and MICHEL E. BERTRAND

Eleven patients with documented coronary spasm were entered prospectively in a study with 4 phases of 2 days each: (1) control, (2) diltiazem or propranolol (mean 225 + 75 mg/day), (3) propranolol or diltiazem (360 mg/day), and (4) propranolol and diltiazem. The effects of the drugs were assessed by the detection of ischemic electrocardiographic episodes (24-hour electrocardiographic monitoring) and provocative tests with ergonovine. During the period of treatment with propranolol, the number and the duration of attacks increased and provocative tests had positive results in all patients. Diltiazem completely abolished spontaneous episodes, but 6 of 11 patients remained sensitive to the administration of ergonovine. The association of the 2 drugs leads to a disappearance of ischemic episodes. In conclusion, the propranolol is ineffective in patients with coronary artery spasm; it can be used in combination with diltiazem, but without any advantage over diltiazem alone.

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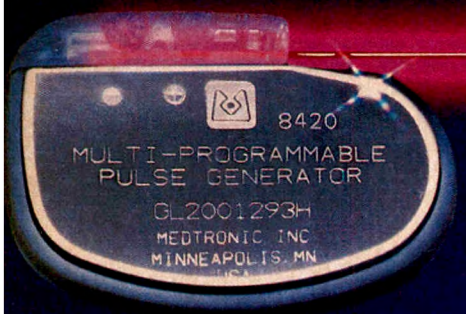

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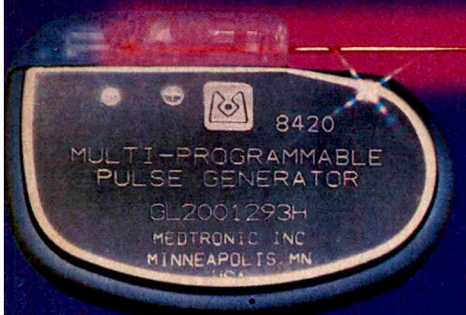

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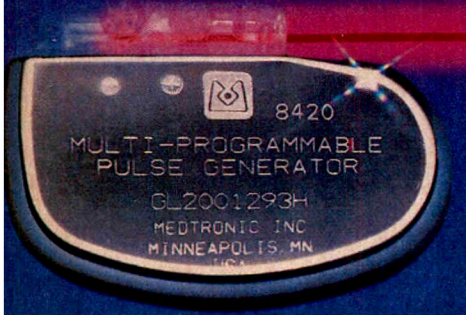
PULSE GENERATOR BATTERY DEPLETION WARNING.

(EOL). 3 distinct warnings signal elective replacement.



Your 70 year old female patient has rushed to your office in alarm. During her routine pulse self-check test, she determined that her pacemaker had dropped 10% in rate. The implanted unit is a Spectrax SXT though, and you are able to reassure her. This rate change is simply a safeguard warning signalling elective replacement. Pulse width on the Spectrax SXT automatically increases to compensate for the gradual decline in battery voltage. She is in no danger of pacemaker battery failure or loss of capture. This fact is easily and visibly confirmed with Spectrax SXT's noteworthy telemetry which prints out battery status on command. In this case the print out has changed from **"Battery OK"** to **Elec. Replace Time!** Seeing is believing. You and your patient have several months in which to make her surgery decision. You can confidently relieve her anxiety.

AX · SXT

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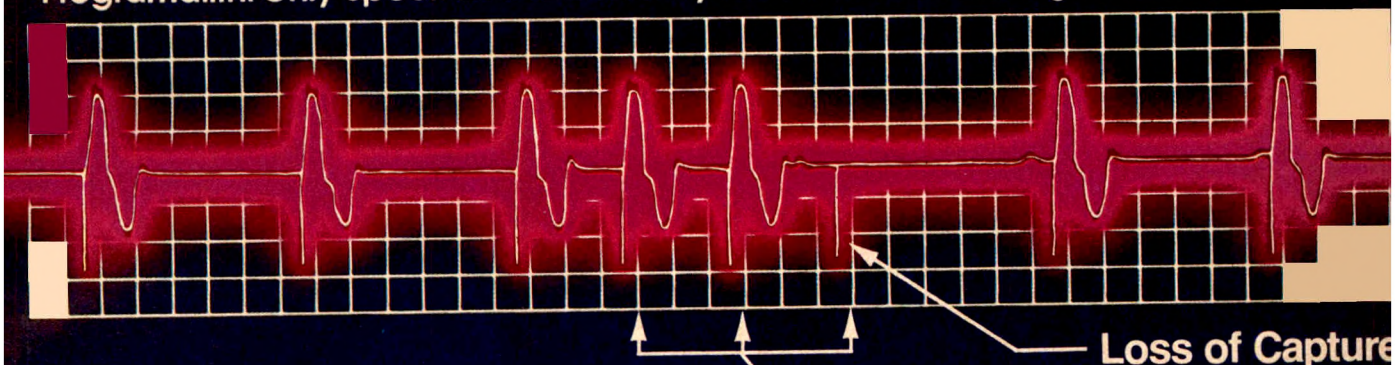

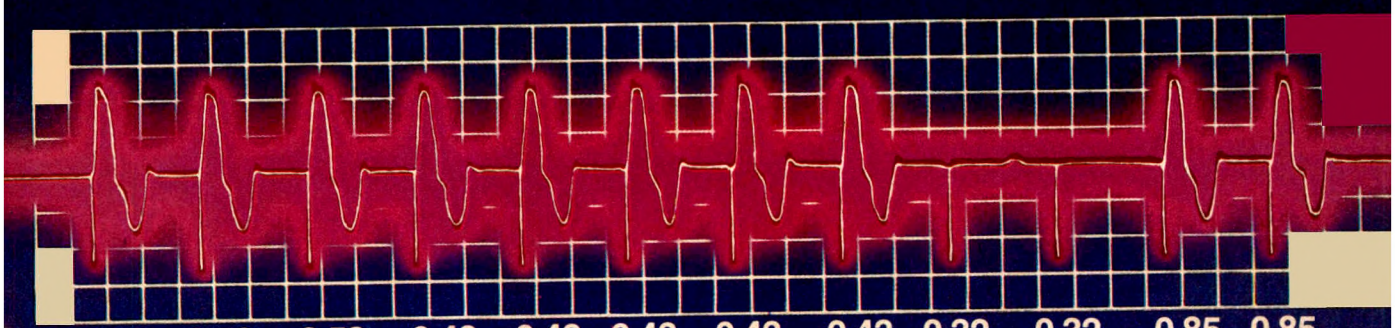


```
SPECTRAX-SXT 8420-23

*TELEMETRY READOUT:*
*     BATTERY OK     *
*        RATE= 70PPM*
*          PW=0.50MS*
*       SENSE= 2.5MV*
*        AMPL=FULL   *
*        HYST=NONE   *
*MAGNET ASYNC MODE *
*        REFR=325MS *
*PERM    DEMAND MODE*
```

```
SPECTRAX-SXT 8420-23

*TELEMETRY READOUT:*
ELECT. REPLACE TIME!
*        RATE= 70PPM*
*          PW=0.50MS*
*       SENSE= 2.5MV*
*        AMPL=FULL   *
*        HYST=NONE   *
*MAGNET ASYNC MODE *
*        REFR=325MS *
*PERM    DEMAND MODE*
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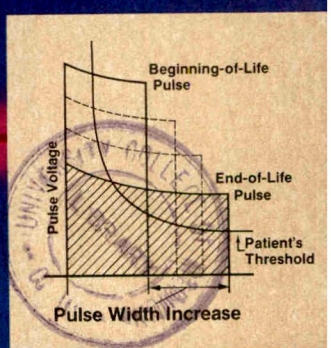

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(Turn this page over for more information)

Medtronic

Medtronic Implantable Pulse Generators and Leads

Intended Uses

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. See the specific precautions and warnings in the technical manuals included with the pulse generator.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

•

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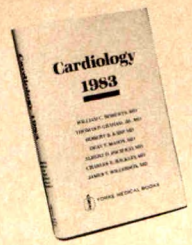
Cardiology 1983



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234 **Long-Term Prognosis After First Q-Wave (Transmural) or Non–Q-Wave (Nontransmural) Myocardial Infarction: Analysis of 593 Patients**

RONALD J. KRONE, ELLEN FRIEDMAN, SAMER THANAVARO, J. PHILIP MILLER, ROBERT E. KLEIGER, and G. CHARLES OLIVER

Follow-up of 593 persons after hospital discharge for a first myocardial infarction was carried out for a mean of 4.7 years. Grouping patients by age, presence or absence of Q waves, and peak serum glutamic oxalacetic transaminase (SGOT) at the time of infarction established 4 groups with distinctly different survivorships. Of the patients who had had Q-wave infarctions, those with an SGOT level <240 IU/liter did better than did those with higher peak SGOT levels, at least for the first 6 months (mortality 3.1 versus 11%). The survivorship of patients who had had non–Q-wave (nontransmural) infarctions was excellent for 2 years (96.8% 2-year survival), but in the third year 12% of the patients older than 60 years of age at the time of their infarct died from cardiac causes, and each successive year an additional 12% of the original survivors died. The implications regarding follow-up strategy and therapy are discussed.

240 **Periods of Differing Mortality Distribution During the First Year After Acute Myocardial Infarction**

ELIZABETH A. GILPIN, JAMES A. KOZIOL, ERLING B. MADSEN, HARTMUT HENNING, and JOHN ROSS, Jr.

Mortality distributions during the first year after acute myocardial infarction (AMI) were analyzed for 3 large, geographically distinct populations using a special statistic to identify periods that exhibited different mortality distributions. The survival curves did not fit a single exponential, and the shapes of the 3 curves were similar. Changepoints in the distributions occurred at days 17, 23, and 24 in the 3 populations and at day 21 for the combined population. In the combined population, the point by which exactly 50% of deaths had occurred was day 19; 75% of the deaths occurred by day 100. These data further define the natural history after AMI and suggest periods appropriate for short- and longer-term interventions aimed at risk reduction.

245 **Validation of Technetium-99m Stannous Pyrophosphate Myocardial Scintigraphy for Diagnosing Acute Myocardial Infarction More Than 48 Hours Old When Serum Creatine Kinase-MB Has Returned to Normal**

HAROLD G. OLSON, KENNETH P. LYONS, SAMUEL BUTMAN, and KENNETH M. PITERS

To assess the feasibility of technetium-99m pyrophosphate scintigraphy in diagnosing acute myocardial infarction (AMI) after serum creatine kinase isoenzyme (CK-MB) has returned to normal, scintigrams were obtained in 107 patients with AMI at the time CK-MB was present, 37 ± 18 hours after the onset of AMI, and at the time CK-MB was absent, 106 ± 34 hours after the onset of AMI. When CK-MB was absent, the sensitivity using either a regional or a diffuse positive scintigram was 95% for transmural AMI and 65% for subendocardial AMI. The sensitivity using a regional positive scintigram was 82% for transmural AMI and 37% for subendocardial AMI. The sensitivity using a high-grade regional positive scintigram was 36% for transmural AMI and 11% for subendocardial AMI. The specificity was 70% for either a regional or a diffuse abnormality, 92% for a regional abnormality, and 100% for a high-grade regional abnormality. It is concluded that pyrophosphate scintigraphy is useful in confirming the diagnosis of AMI, particularly transmural, for an infarct >48 hours old when CK-MB has returned to normal. A positive scintigram with a high-grade regional abnormality is specific for a recent AMI and may contribute to establishment of the diagnosis when lactic dehydrogenase isoenzymes are inconclusive.

252 **Evaluation of Serial QRS Changes During Acute Inferior Myocardial Infarction Using a QRS Scoring System**

CHRISTINE I. ANDERSON, DAVID G. HARRISON, NANCY C. STACK, NANCY B. HINDMAN, RAYMOND E. IDEKER, SEBASTIAN T. PALMERI, RONALD H. SELVESTER, and GALEN S. WAGNER

The evolution of changes in the QRS complex during the 3 days after the onset of an initial inferior myocardial infarction was studied in 82 consecutive patients. Each patient's standard 12-lead electrocardiograms were assigned points (a QRS score) according to the absolute duration of the Q and R waves and the amplitude ratios of R-to-Q and R-to-S waves. This QRS score has been demonstrated to correlate ($r = 0.74$) with the anatomic extent of single inferior myocardial infarcts. By this system, 43 patients (53% of the study group) had an initial ECG that registered a score of 0 and developed QRS points only after admission. The QRS scores of 18 additional patients (22% of the study group) were observed to change after admission. Forty-nine score changes were noted on day 2 and 18 on day 3. All of these changes resulted in an increase in QRS score. Thus, there is a distinct pattern to the evolution of QRS changes during inferior infarction that results in sequential increases in a QRS score based upon electrocardiographic indicators of the extent of myocardial necrosis.

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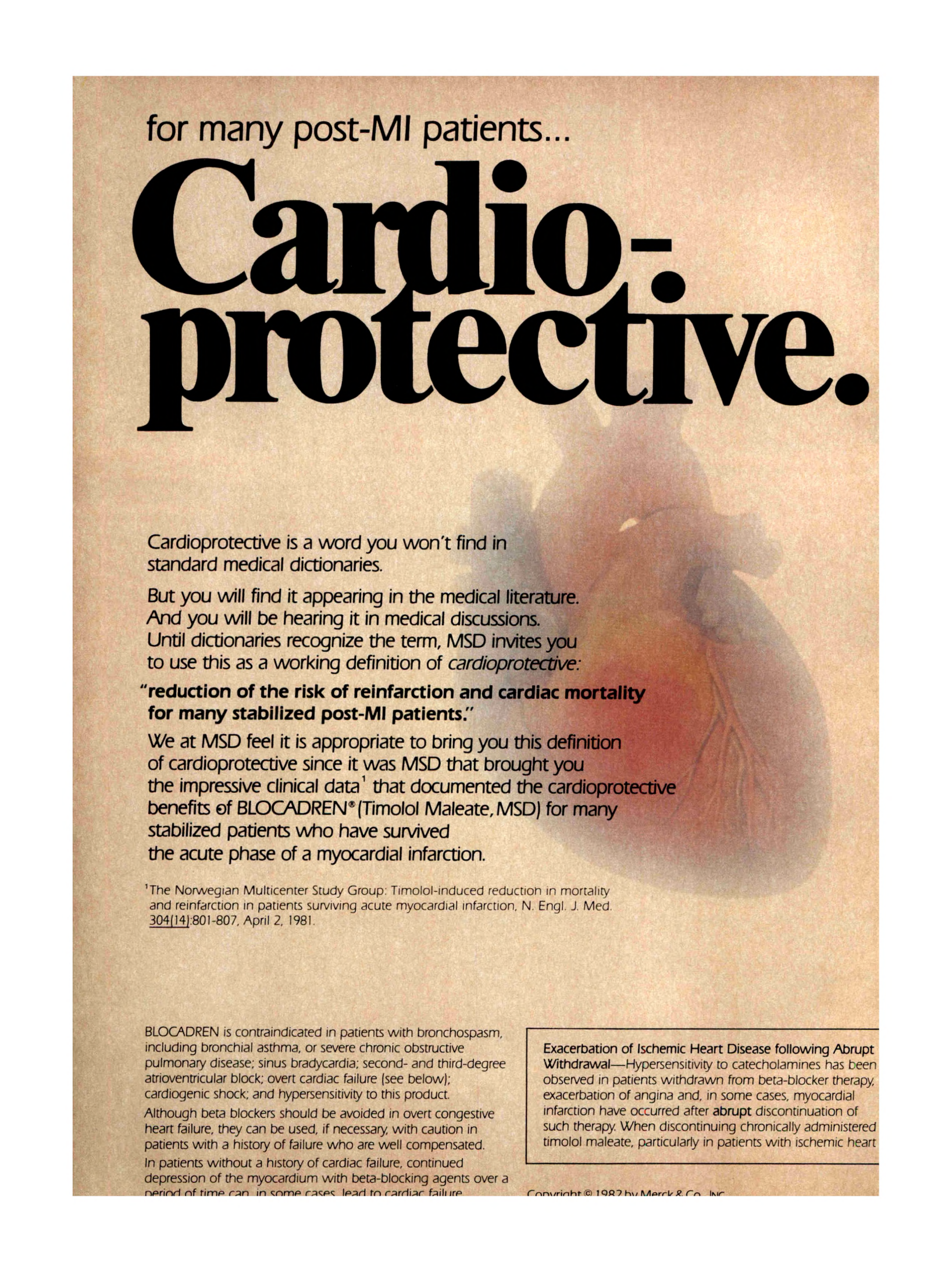

Cardioprotective is a word you won't find in standard medical dictionaries.

But you will find it appearing in the medical literature. And you will be hearing it in medical discussions. Until dictionaries recognize the term, MSD invites you to use this as a working definition of *cardioprotective:*

"reduction of the risk of reinfarction and cardiac mortality for many stabilized post-MI patients."

We at MSD feel it is appropriate to bring you this definition of cardioprotective since it was MSD that brought you the impressive clinical data[1] that documented the cardioprotective benefits of BLOCADREN® (Timolol Maleate, MSD) for many stabilized patients who have survived the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after **abrupt** discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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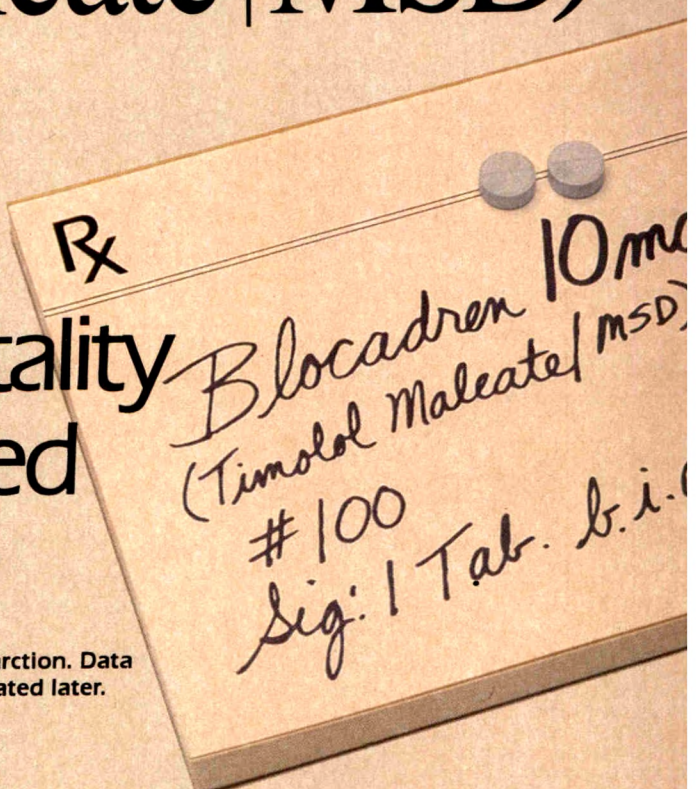
reduces the risk of reinfarction and cardiac mortality for many stabilized post-MI patients



Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.

disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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(TIMOLOL MALEATE | MSD)

CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: *Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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257 Coronary and Left Ventricular Angiographic Anatomy and Prognosis of Survivors of First Acute Myocardial Infarction

ROBERT D. ABRAHAM, GARETH S. ROUBIN, PHILLIP J. HARRIS, LOUIS BERNSTEIN, and DAVID T. KELLY

To relate coronary anatomy and left ventricular (LV) function to prognosis, 197 of 269 consecutive survivors of a first myocardial infarction (MI) who were <60 years old underwent prospective cardiac catheterization a median of 2 weeks after admission and were followed up for a median 24 months (range 12 to 61). Seventy-two patients were excluded from angiography because of early death (9), severe noncoronary disease (44), MI complications (6), or patient refusal (13). The prevalence of multivessel disease was low (30%) and unrelated to the site of MI or the presence of Q waves but was higher in patients with previous angina pectoris ($p = 0.05$) or in those in Killip class II or III ($p = 0.02$). There were only 8 deaths from cardiac causes. The survival rate at 12 months was 97 ± 1% and at 24 and 36 months, 95 ± 2%. Nineteen patients underwent coronary revascularization surgery. Because the number of deaths was small, the differences in survival between patients with single or multivessel disease and normal or depressed ejection fractions failed to reach significance. Survivors of first MI <60 years old have a low prevalence of multivessel disease and a good prognosis.

261 Coronary Arterial Aneurysm Formation After Balloon Angioplasty

JAMES A. HILL, JAMES R. MARGOLIS, ROBERT L. FELDMAN, C. RICHARD CONTI, and CARL J. PEPINE

Previously described complications of percutaneous transluminal coronary angioplasty (PTCA) do not include coronary arterial aneurysm formation. Five patients with coronary arterial aneurysm formation at the site of PTCA are described. Aneurysms were found 11 days to 4 months after PTCA. Before PTCA, all patients were in New York Heart Association functional class III or IV and in 2 patients, myocardial infarctions with acute coronary occlusion were evolving. Evidence for intimal disruption or abrupt reocclusion was present in the other 3 patients after PTCA. Four of the 5 patients had angina at the time of the follow-up catheterization that identified the aneurysm from 11 days to 4 months after PTCA. Possible mechanisms of aneurysm formation and its relationship to healing are discussed.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

265 The Automatic Implantable Defibrillator: Local Ventricular Bipolar Sensing to Detect Ventricular Tachycardia and Fibrillation

ROGER A. WINKLE, STANLEY M. BACH, Jr., DEBRA S. ECHT, CHARLES D. SWERDLOW, MIR IMRAN, JAY W. MASON, PHILIP E. OYER, and EDWARD B. STINSON

The first generation automatic implantable defibrillator implanted in man reliably detected ventricular fibrillation and sinusoidal ventricular tachycardia, but failed to sense all nonsinusoidal ventricular tachycardias. To solve this problem, a new ventricular tachycardia detection scheme was developed using a local ventricular bipolar electrogram and electronic circuits using rate averaging and automatic gain control. This detection scheme was tested during electrophysiologic studies in 11 patients with ventricular tachycardia and fibrillation. All 22 episodes of induced ventricular tachycardia with a rate above the selected cutoff were detected after an average of 5.1 ± 1.8 seconds. Arrhythmia detection and signal quality in 9 patients who received automatic defibrillators using the new bipolar circuit were compared with the findings in 5 patients who previously received first generation units. The newer bipolar units had shorter and more uniform sense times (5.5 ± 1.4 versus 12.2 ± 7.1 seconds). It is concluded that malignant ventricular tachyarrhythmias can be accurately sensed using bipolar rate detection and that this system has significant advantages over the previously used detection scheme.

271 Effects of Oral Diltiazem in Paroxysmal Supraventricular Tachycardia

SAN-JOU YEH, HWAI-CHENG KOU, FUN-CHUNG LIN, JUI-SUNG HUNG, and DELON WU

The effects of oral diltiazem on induction and sustenance of paroxysmal supraventricular tachycardia were evaluated in 36 patients, 24 with atrioventricular (AV) reentrance incorporating an accessory pathway and 12 with AV nodal reentrance. Diltiazem prevented induction or sustenance of tachycardia in 20 of the 24 patients with AV reentrance, due to increased anterograde normal pathway refractoriness in 19 patients and increased retrograde accessory pathway refractoriness in 1 patient. It prevented induction or sustenance of tachycardia in 8 of the 12 patients with AV nodal reentrance, due to increased anterograde slow pathway refractoriness in 2 patients and increased retrograde fast pathway refractoriness in 6. Thus, oral diltiazem may be used as an alternative antiarrhythmic agent for prophylaxis of paroxysmal supraventricular tachycardia.

Continued on page A28

279 **Effect of Procainamide on Dispersion of Ventricular Refractoriness**

JAY A. SHECHTER, RUTH CAINE, TED FRIEHLING, PETER R. KOWEY, and

Ventricular arrhythmias after Q-T prolongation by drugs could result from a nonhom toriness (dispersion). Dispersion of effective refractory periods (ERP) was measur procainamide. Procainamide prolonged ERP in drive by an average of 30 ms ($p < 0$ 50 ms ($p < 0.001$). Procainamide did not alter measured dispersion (54 ± 16 to 44 ± to 47 ± 13 ms in drive). Polymorphic ventricular tachycardia (VT) was induced in 6 generally failed to reduce dispersion; less polymorphic tachycardia after procainam rowed dispersion. Polymorphic VT was not induced after procainamide in 2 patients sades de pointes caused by type I drugs. The mechanism of torsades was not expla toriness or by polymorphic VT initiated by premature beats after a type I drug.

283 **Exercise-Induced Bundle Branch Block**

VICTOR S. WAYNE, RICHARD L. BISHOP, LINDA COOK, and DAVID H. SPC

To investigate exercise-induced bundle branch block (BBB), clinical, electrocardiogr ic, scintigraphic, and follow-up data were analyzed in 16 patients, 11 with exercis Fourteen had a preexisting electrocardiographic abnormality—11 had either incom traventricular conduction delay. Heart rates of exercise BBB onset varied from 7(tients, onset and offset rates appeared to be related (within 8 beats/min). Of the 16 tery disease (CAD), 2 cardiomyopathy, 2 probable coronary spasm, 1 ventricular arr and 1 had no cardiac disease. Three patients had reversible thallium perfusion defe concurrent with development of exercise BBB. Three patients in whom exercise B a mean of 28 months of follow-up, 2 patients died of noncardiac causes and 1 had a tion. Thus, exercise-induced BBB primarily occurs in cardiac disease, mostly CAD; tate against CAD.

287 **Pacemaker-Mediated Tachycardias: A Rapid Bedside Technique for Induction**

PHILIP O. LITTLEFORD, R. CHARLES CURRY, Jr., KERRY M. SCHWARTZ, an

Thirty-one patients who underwent DDD pacemaker implantation were evaluated f loatrial conduction. Ventriculoatrial conduction was found in 17 patients using a sir tection of ventriculoatrial conduction was uniformly associated with pacemaker tachycardia was prevented by manipulation of the atrial refractory period. When ver present over the follow-up period, it was remarkably constant in duration but disapp failure or antiarrhythmic therapy.

292 **Intermittent Preexcitation in the Wolff-Parkinson-White Syndrome**

GEORGE J. KLEIN and SAJAD S. GULAMHUSEIN

The prevalence of intermittent preexcitation in 52 consecutive patients with Wolff was determined by reviewing electrocardiogram, ambulatory monitoring and treadr electrophysiologic testing to determine the electrophysiologic correlates of this p tients, 50% had intermittent loss of the delta wave. These patients had longer effect accessory pathway (356 ± 114 vs 295 ± 29 ms, $p < 0.05$) and longer shortest cycle terograde conduction (426 ± 171 vs 291 ± 63 ms, $p < 0.02$) than their counterpa wave. During atrial fibrillation, 85% of the patients with intermittent loss of the delta vals between preexcited beats >250 ms, versus 50% of patients with constant pre data support the hypothesis that intermittent loss of the delta wave suggests a beni atrial fibrillation.

SYSTEMIC HYPERTENSION

297 **Malignant Hypertension in Women Aged 15 to 44 Years and Its Relation to Cig Oral Contraceptives**

DIANA B. PETITTI and ARTHUR L. KLATSKY

To study the factors associated with malignant hypertension in young women, the m age 15 through 44 years who were hospitalized in any of 15 affiliated hospitals in 197 nant hypertension were reviewed. There were 15 new patients in this period, an in

Continued on page A36

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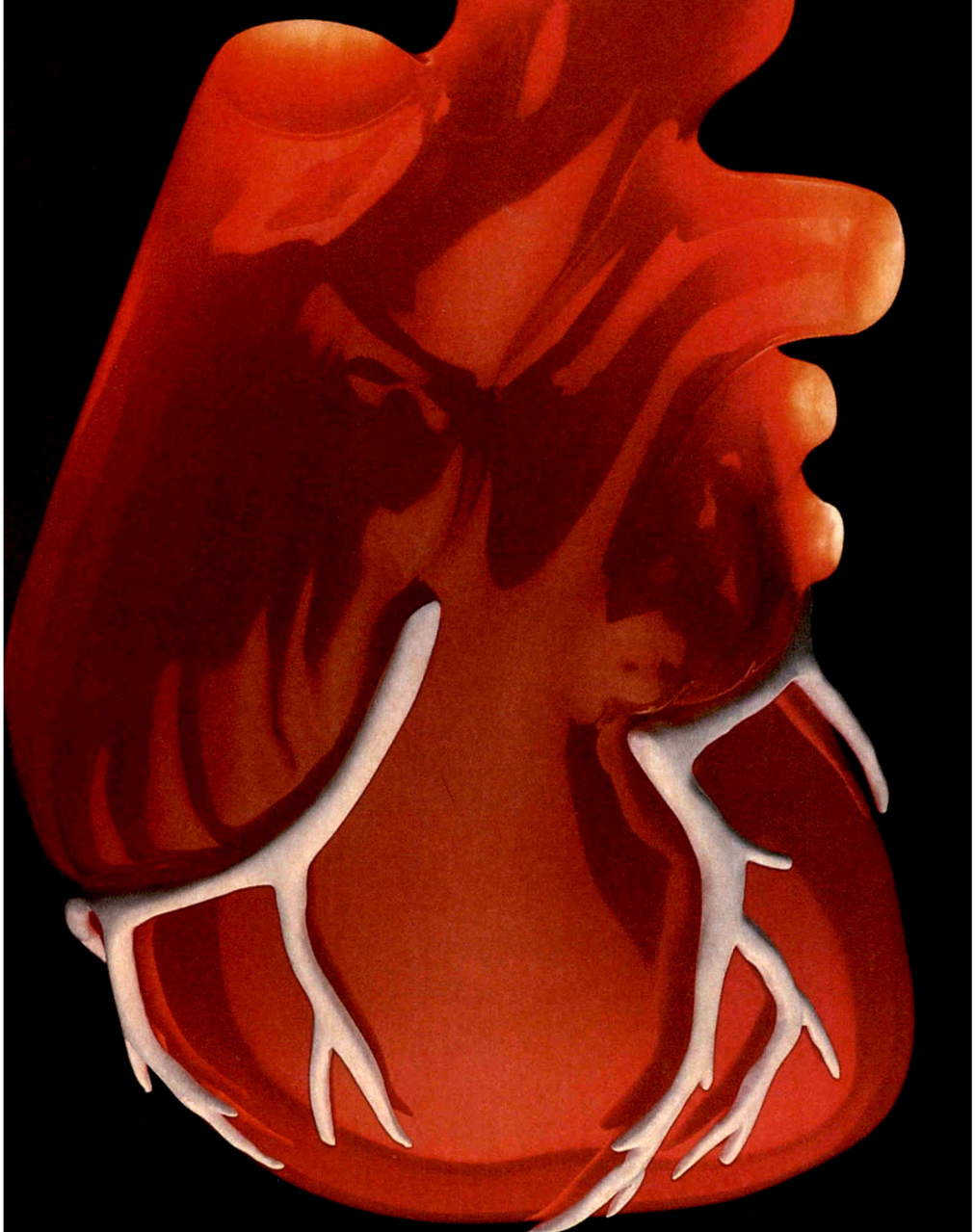

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CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

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Indications

(1) Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm.

(2) Cardizem is indicated in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

ANTIANGINAL MECHANISM OF ACTION

- Produces relaxation of coronary vascular smooth muscle
- Dilates both large and small coronary arteries at drug levels that cause little or no negative inotropic effect
- Produces dose-dependent decreases in peripheral resistance
- Resting heart rate is usually unchanged or slightly reduced

Reduces the pressure/rate product for any given work load in patients with effort-associated angina

3, Marion Laboratories, Inc.

CARDIZEM™ (diltiazem HCl) offers a distinctive profile of effects

(1) Vascular smooth-muscle relaxation with a potent effect on the coronary arteries.[1]

(2) Mild effect on afterload reduction.

(3) In normotensive patients at rest, recommended dosage levels producing coronary vasodilation result in only a mild reduction in diastolic blood pressure and no change in heart rate.

(4) At submaximal exercise, it causes a reduction in heart rate and mean blood pressure compared with placebo, thus reducing myocardial oxygen demand and permitting patients to exercise significantly longer.

(5) Increases coronary blood flow.

(6) Little or no negative inotropic effect at recommended doses while providing a powerful inhibition of coronary artery spasm.

(7) A positive effect on left ventricular function in patients with reduced left ventricular ejection fraction.[2]

(8) Increases ejection fraction at both submaximal and maximal exercise. Exercise ejection fraction is especially increased in patients with poor ventricular function.[3]

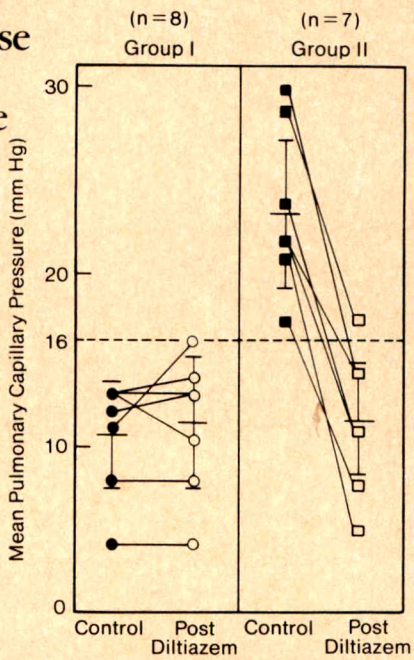
While Cardizem tends to prolong AV conduction,* only rarely has there been an increase in PR intervals outside of normal limits.

*See Contraindications and Warnings.

CARDIZEM™ (diltiazem HCl) tends to normalize stress-induced increases in pulmonary capillary pressure (PCP)

The effect of a single 120-mg† dose of Cardizem was evaluated on symptom-limited upright exercise in 15 patients with effort angina.[4]

†It should be noted that this study employed a single 120-mg dose of diltiazem for hemodynamic measurement purposes. The approved maximum dose for Cardizem is 240 mg given in divided doses, three to four times daily.



CHANGE IN FILLING PRESSURE AT MAXIMAL EXERCISE[4]

Patients with control PCPs in normal range at maximal exercise showed little change in these values following diltiazem (Group I). Patients with markedly elevated control PCPs at maximal exercise (>16 mm Hg) showed dramatic reductions in these values following diltiazem (Group II).

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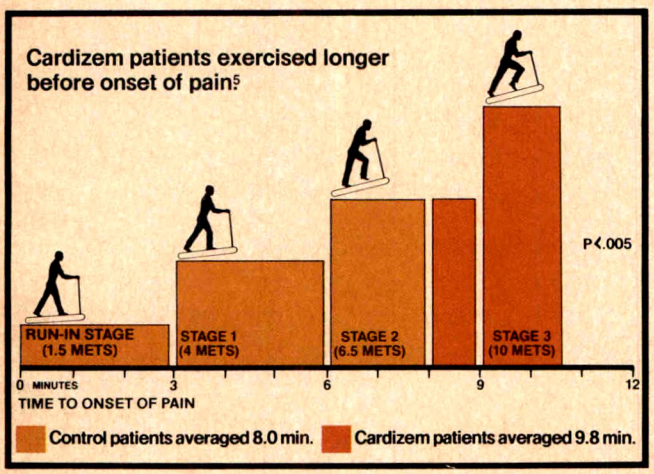
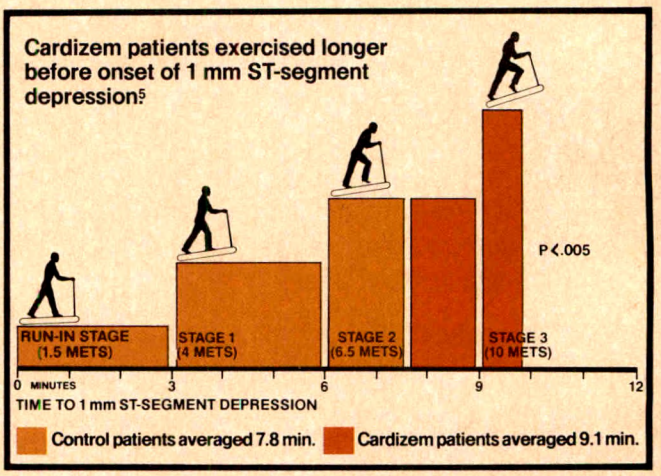
EXCELLENT CLINICAL RESPONSE TO CARDIZEM™ (diltiazem HCl) IN THE MANAGEMENT OF CLASSIC EFFORT ANGINA

CARDIZEM™ (diltiazem HCl) allows angina patients to significantly prolong exercise tolerance, even in demanding Bruce protocol exercise tests[5] (n=15)*





Protocol:

A Bruce protocol with a run-in stage was used. Each stage lasts three minutes.

Succeeding stages represent such an increase in speed and slant of the treadmill that each minute spent in a succeeding stage represents a highly significant increase in metabolic equivalents (METS). For example, METS expenditure in run-in stage of the protocol (0 to 3 min) is 1.5. METS expenditure of stage 1 (3 to 6 min) is 4.0. Stage 2 (6 to 9 min) expenditure is 6.5, and stage 3 (9 to 12 min) is 10.

The study[5,6] was double-blind, randomized, triple cross-over comparing diltiazem with placebo, lasting 7 weeks.

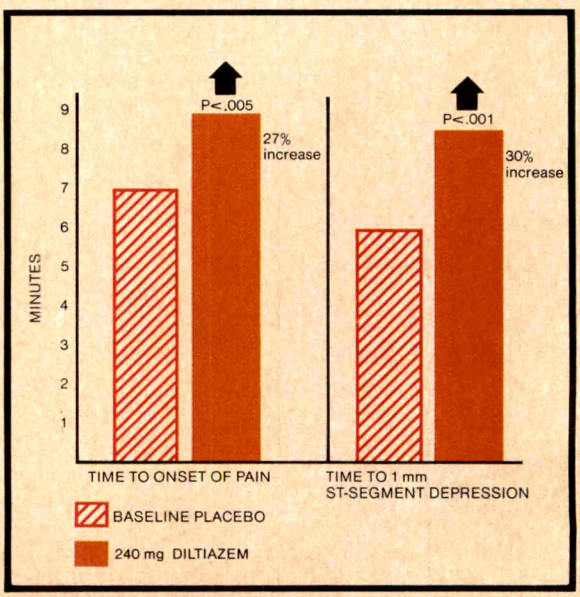
5. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78(July suppl): 234-238, 1980.

6. Hossack KF, Pool PE, Steele P, et al: Efficacy of diltiazem in angina on effort: A multicenter trial. *Am J Cardiol* 49:567-572, 1982.

*This study is a report from one center in a multicenter study.

CARDIZEM™ (diltiazem HCl) produced marked angina improvement in multicenter study[6]

- 27% increase in time to onset of pain
- 30% increase in time to ST-segment depression



RESULTS OF 57 PATIENTS EVALUATED IN A MULTICENTER STUDY[6]

CARDIZEM™ (diltiazem HCl) PRODUCED SIGNIFICANT DECREASE IN EFFORT ANGINA ATTACKS COMPARED WITH PLACEBO IN 63-PATIENT DIARY STUDY[7]

Cardizem therapy resulted in a mean reduction of 5.3 attacks per week during weeks 7 and 8, compared with a mean reduction with placebo of 2.0 attacks per week.

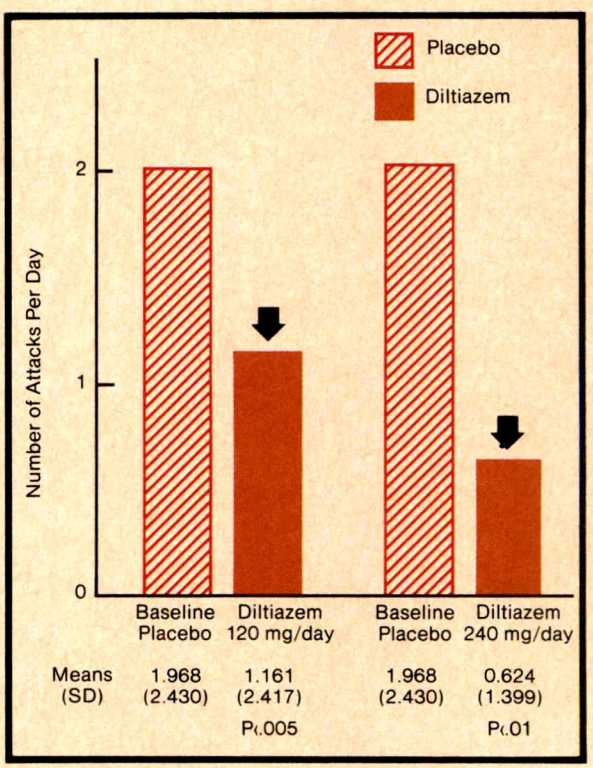
During weeks 9 and 10, Cardizem therapy resulted in a mean reduction of approximately 5.9 attacks per week compared with a mean reduction of 2.5 attacks per week with placebo.

41% TO 68% REDUCTION IN FREQUENCY OF PRINZMETAL'S VARIANT ANGINA ATTACKS WITH CARDIZEM™ (diltiazem HCl)[8]

Mean attack rate during 120-mg/day dosage period was reduced 41% from baseline period. In 240-mg/day phase, decrease with Cardizem was 68%. This shows a positive dose-related response.

75% reduction in attack rate reported in 13-patient, cross-over, placebo-controlled study[1]

71% reduction in attack rate reported in 11-patient, cross-over, placebo-controlled study[9]



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9. Pepine CJ, Feldman RL, Whittle J, et al: Effect of diltiazem in patients with variant angina: A randomized double-blind trial. *Am Heart J* 101:719-725, 1981.

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LOW INCIDENCE OF SIDE EFFECTS WITH CARDIZEM™ (diltiazem HCl)

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with CARDIZEM™ (diltiazem HCl) have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

In many cases, the relationship to Cardizem has not been established.

Other reactions infrequently reported (<1.0%) during supervised trials were:

- Cardiovascular: Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart
- Central Nervous System: Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations
- Gastrointestinal: Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis
- Dermatologic: Pruritus, petechiae, urticaria
- Other: Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain

Of those adverse reactions reported, the most severe were:
A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of Cardizem.

Experience in 959 patients taking oral doses of Cardizem resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during Cardizem therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

PROFESSIONAL USE INFORMATION

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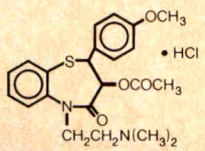
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (4 of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem t.i.d. of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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1/83

women of these ages per year. Four women had underlying renal disease. Of the other 11 women, all used oral contraceptives, smoked cigarettes, or both. Nine were white; 6 women had normal blood pressure in the 24 months before hospitalization.

CONGESTIVE HEART FAILURE

299 Determinants of Circulatory Response to Intravenous Hydralazine in Congestive Heart Failure

JOHN R. WILSON, MARTIN ST. JOHN SUTTON, J. SANFORD SCHWARTZ, NANCY FERRARO, and NATHANIEL REICHEK

The factors that determine the circulatory response to hydralazine were investigated in 28 patients with chronic left ventricular (LV) dysfunction. Hemodynamic data and echocardiographic LV end-diastolic dimension were correlated with the response to 20 mg of intravenous hydralazine and to a dose titrated to reduce systemic resistance (SVR) ≥20%. Hydralazine, 20 mg, decreased SVR (from 23 ± 8 to 18 ± 8 U [$p < 0.01$]) and increased cardiac index (from 2.0 ± 0.5 to 2.5 ± 0.6 liters/min/m^2 [$p < 0.01$]) and stroke work index (SWI) (from 21 ± 11 to 24 ± 9 g·m/m^2 [$p < 0.05$]). Titrating the dose increased the cardiac index further to 2.7 ± 0.6 liters/min/m^2 and SWI to 32 ± 9 g·m/m^2. The change in SVR produced by 20 mg of hydralazine correlated only with initial SVR ($r = 0.53$). The percent change in SWI produced by 20 mg of hydralazine correlated directly with end-diastolic wall stress ($r = 0.69$) and pulmonary wedge pressure ($r = 0.43$) and inversely with SWI ($r = -0.49$). Similar correlations were observed when the dose of hydralazine was titrated. The response to hydralazine did not correlate with LV end-diastolic dimension or right atrial pressure. Thus, the vascular response to moderate doses of hydralazine is related to initial SVR, whereas LV pump response is related to the level of initial LV pump dysfunction.

304 Amrinone Therapy for Congestive Heart Failure in Outpatients With Idiopathic Dilated Cardiomyopathy

CARL V. LEIER, KAREN DALPIAZ, PATRICIA HUSS, JAMES B. HERMILLER, RAYMOND D. MAGORIEN, THOMAS M. BASHORE, and DONALD V. UNVERFERTH

Chronic dosing of amrinone in 13 patients with moderate to severe congestive heart failure effected a modest, but significant, improvement in exercise tolerance compared with a comparable control group. Amrinone did not improve functional classification, noninvasive indexes of LV function or exercise ejection fraction above control values. All patients who received amrinone experienced at least 1 symptom-related or laboratory-detected side effect.

VALVULAR HEART DISEASE

309 Echocardiographic Evaluation of Porcine Bioprosthetic Valves: Experience With 309 Normal and 59 Dysfunctioning Valves

MOHSIN ALAM, JEFFREY B. LAKIER, SOL D. PICKARD, and SIDNEY GOLDSTEIN

To determine the clinical value of echocardiography in the evaluation of porcine bioprosthetic valves, we analyzed adequate-quality echocardiographic studies of 309 normal and 59 dysfunctioning valves. Valve dysfunction resulted from spontaneous cusp degeneration in 39 (34 valve regurgitations, 5 stenoses), infective endocarditis in 12, paravalvular regurgitation in 5, and regurgitation of redundant cusps, mitral valve thrombi, and aortic stent stenosis in 3 others. Echocardiographic findings were correlated with pathology for 45 of 59 dysfunctioning valves. Echocardiographic abnormalities were demonstrated in 41 of 59 (69%) dysfunctioning valves. A systolic mitral or diastolic aortic valve fluttering was diagnostic of a regurgitant valve due to torn or unsupported cusp margin and was observed in 28 of 34 (82%) regurgitant valves. Echocardiographic cusp thickness of ≥3 mm correctly identified all regurgitant and stenotic valves with gross anatomic evidence of cusp thickening or calcific deposits. Echocardiographic valve abnormalities were observed in only 4 of 12 patients with infective endocarditis and 1 of 5 with paravalvular regurgitation.

316 Abnormal Cardiovascular Regulation in the Mitral Valve Prolapse Syndrome

F. ANDREW GAFFNEY, BRUCE C. BASTIAN, LYNDA B. LANE, W. FRED TAYLOR, JURETA HORTON, JAMES E. SCHUTTE, ROBERT M. GRAHAM, WILLIAM PETTINGER, and C. GUNNAR BLOMQVIST, *With the technical assistance of* WILLIE E. MOORE, Jr.

Studies of patients with the mitral valve prolapse (MVP) syndrome suggest autonomic nervous system dysfunction, but a precise definition of mechanisms is lacking. In this study, supine and standing heart rate, blood pressure, cardiac output, oxygen consumption, plasma catecholamine levels, and plasma volume were measured in 23 women with MVP and in 17 normal control subjects. An analysis of the hemodynamic state at rest and the

Continued on page A39

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for Anxiety

See important information on following page.

*All benzodiazepines produce additive sedative effects when given with alcohol or other CNS depressants.

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NEW TABLET DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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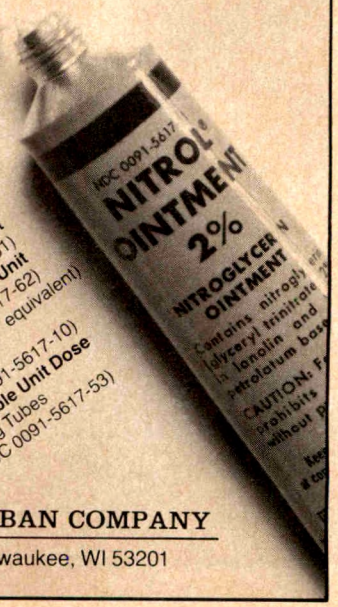

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postural responses revealed 2 distinct subgroups of patients; those with a normal heart rate but increased vasoconstriction (Group I, n = 10) and those with orthostatic tachycardia (Group II, n = 13). The supine heart rate in Group I patients and control subjects was virtually identical, 78 ± 3 and 79 ± 2 beats/min, respectively, compared with Group II patients, who had a heart rate (supine) of 97 ± 3 beats/min. Estimated total blood volumes were lowest in Group I patients, intermediate in Group II patients, and highest in control subjects ($p < 0.05$). After standing for 5 minutes, patients had a higher mean plasma epinephrine value, diastolic blood pressure (81 ± 2 versus 74 ± 3 mm Hg, $p < 0.05$) and peripheral resistance (1,878 ± 114 versus 1,414 ± 92 units, $p < 0.01$), wider calculated arteriovenous oxygen difference (6.7 ± 0.4 versus 5.3 ± 0.5 units, $p < 0.05$), and lower stroke volume index (26 ± 2 versus 33 ± 2 units, $p < 0.01$) than did the control subjects. Cardiac output was normal in Group II patients but reduced in the Group I patients, who demonstrated marked vasoconstriction. No patient had evidence of a "hyperkinetic" circulatory state. These symptomatic patients with MVP with subnormal stroke volumes maintained arterial pressure with either tachycardia or vasoconstriction. Increased plasma catecholamine levels were associated with a reduced blood volume. A cycle of decreased forward stroke volume, vasoconstriction, and blood volume contraction appears to be present.

CARDIOMYOPATHY

321 Noncardiovascular Findings Associated With Heart Disease in the Idiopathic Hypereosinophilic Syndrome

JOHN B. HARLEY, ANTHONY S. FAUCI, and HARVEY R. GRALNICK

Endomyocardial fibrosis is a major complication of the idiopathic hypereosinophilic syndrome. The noncardiovascular findings from a group of 50 patients are described that differentiate those in whom overt heart disease develops from those who remain free of heart disease. Patients with the idiopathic hypereosinophilic syndrome and heart disease are more likely to have characteristics of a myeloproliferative disorder, to be male, and to carry the Bw44 histocompatibility locus antigen. Patients who remain free of heart disease are more likely to have characteristics of an allergic disease and to be female. These results should help to identify patients at risk for the development of overt heart disease in the idiopathic hypereosinophilic syndrome.

CONGENITAL HEART DISEASE

325 Two-Dimensional Echocardiographic Assessment of Surgically Closed Ventricular Septal Defect

JOSE L. ANDRADE, WALTER SERINO, MARC de LEVAL, and JANE SOMERVILLE

In this study, 120 patients operated on for closure of a ventricular septal defect (VSD) were assessed echocardiographically. Echocardiographic findings of intact ventricular septum (VS) or residual shunt were correlated with angiographic findings in 30 patients and with clinical signs in 90 patients. Apart from minute shunts not detected echocardiographically and a few persistent small "drop-outs," probably due to peripatch edema or malalignment of the VS, wrongly interpreted as residual shunt, 2-dimensional echocardiography was a reliable noninvasive technique for detecting significant residual shunt and intact VS after surgical closure of VSD.

330 Postmortem Digoxin Tissue Concentration and Organ Content in Infancy and Childhood

ALOIS R. HASTREITER and RONALD L. VAN DER HORST

Postmortem tissue samples from 36 infants and children were analyzed for digoxin concentration. Dosage, duration and mode of administration were evaluated. Blood and tissue levels were generally higher in small infants than in older children and adults. Although toxicity was not studied, based on the therapeutic distributions observed, blood, liver, myocardium and probably skeletal muscle were felt to be the best markers for the evaluation of toxicity. Renal tissue was not considered reliable because of marked variability of digoxin concentration. Maximal therapeutic concentrations were twice as high in some tissue samples of premature and full-term neonates than in those from older children.

336 Masked Subaortic Stenosis in Ostium Primum Atrial Septal Defect: Recognition and Treatment

RHONDA S. LAPPEN, ALEXANDER J. MUSTER, FAROUK S. IDRISS, THOMAS W. RIGGS, MICHEL ILBAWI, MILTON H. PAUL, SAROJA BHARATI, and MAURICE LEV

Severe subaortic stenosis may be masked hemodynamically in ostium primum defect because of left ventricular systolic regurgitation into the right and left atria and a mobile cleft septal mitral leaflet. Such potential stenosis can be recognized morphologically by angiography and echocardiography before corrective surgery. Five patients who demonstrated subaortic pressure gradients (mean 56 mm Hg) postoperatively had characteristic systolic narrowing of the left ventricular outflow tract (goose-neck deformity), whereas goose-neck deformity narrowing is observed only during diastole in a typical case of ostium primum defect. This outflow narrowing is a re-

Continued on page A42

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A-V sequential pacing is specifically indicated for treatment of conduction disorders that require restoration of both rate and atrio-ventricular synchrony. A-V sequential pacing may also be indicated for patients with extensive myocardial infarction with A-V block and sinus bradycardia.

CONTRAINDICATIONS AND SIDE EFFECTS: There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

PRECAUTIONS: See the "Cautionary notes" section of the Physicians Manual for the Intermedics cardiac pluse generator to be implanted. Discussion includes Possible Complications, Environmental Hazards (electrocautery, diathermy, defibrillation, therapeutic radiation, home appliances, and industrial and special environments), and Effects of Drugs.

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sult of extensive excavation of the posterior smooth ventricular septum and an abnormally anterior and medial attachment of the mitral anulus that fills this gap in the septum. Additional obstruction may be produced by discrete fibrous ridges and poor mitral valve attachments. Surgical treatment includes resection of discrete obstructive elements, enlargement of the outflow tract and, rarely, replacement of the mitral valve.

341 **Mechanisms of Closure of Perimembranous Ventricular Septal Defect**

ROBERT H. ANDERSON, CORA C. LENOX, and JAMES R. ZUBERBUHLER

A series of hearts with an isolated perimembranous ventricular septal defect were examined for signs of partial closure by discrete anatomic structures. Twenty-six hearts (38%) showed evidence of partial occlusion, most often by tricuspid valve leaflets or structures derived from the tricuspid valve. Only 2 hearts showed any sign of closure by an aneurysm of the membranous septum. Perimembranous defects extending into the inlet or trabecular septum, or both, were commonly partially occluded; defects extending into the outlet septum never were.

346 **Two-Dimensional Echocardiographic Appearance of Complete Left-Sided Juxtaposition of the Atrial Appendages**

ALVIN J. CHIN, FREDRICK Z. BIERMAN, ROBERTA G. WILLIAMS, STEPHEN P. SANDERS, and PETER LANG

This report describes the 2-dimensional echocardiographic appearance of left-sided juxtaposition of the atrial appendages (JAA). Between January 1, 1978, and June 30, 1979, 2 infants had the diagnosis of left-sided JAA at autopsy. Review of the echocardiographic studies of these 2 patients revealed that the septum secundum was oriented posteriorly in the transverse view of the atria. From July 1979 to June 1981, prospective evaluation of all infants for the presence of this finding revealed it in 2 additional patients. Left-sided JAA was confirmed at surgery in 1 case and by selective right atrial angiography in the other. Thus, the diagnosis of left-sided JAA has important implications for both atrial baffle operations and for the Fontan procedure.

349 **Growth and Tissue Abnormalities in Young People With Cyanotic Congenital Heart Disease Receiving Systemic–Pulmonary Artery Shunts**

DAVID BAUM, REBECCA Q. BECK, and WILLIAM L. HASKELL

The effects of systemic–pulmonary artery shunts on growth, body composition and adipose tissue were studied in 29 children, aged 2 to 16 years, with cyanotic congenital heart disease. Sixteen of these patients received surgical shunts and 13 were unoperated. Postoperatively, all shunted patients were better oxygenated and were symptomatically improved. However, the groups were not significantly different in height, weight, lean body mass, total body fat, lean/fat ratio, cellular lipid content or total number of lipid-containing fat cells. Age at operation did not appear to influence the effects of surgery. These observations suggest that growth and certain measurements of tissue development were unaffected by surgical systemic–pulmonary artery shunts despite increased oxygenation and symptomatic improvement after operation.

353 **The Marfan Syndrome in Early Childhood: Analysis of 15 Patients Diagnosed at Less Than 4 Years of Age**

HENDRICA E. SISK, KENNETH G. ZAHKA, and REED E. PYERITZ, *With the technical assistance of* CATHY HENSLEY

To appreciate more completely the Marfan syndrome in early childhood, the clinical and echocardiographic features of 15 children diagnosed at <4 years of age were reviewed. Two children were lost to follow-up study, but in the 13 who were followed up, all had echocardiographic evidence of increasing aortic root dimension at a rate generally greater than predicted on the basis of increasing body surface area. Only 1 patient had aortic regurgitation and none required aortic surgery. All patients had mitral valve prolapse. Progressive mitral valve dysfunction was seen in 70% of patients and 4 required mitral valve replacement. These observations suggest that in children with Marfan syndrome, (1) aortic root dilatation is usually present early and serves as an objective indicator of the syndrome, and (2) mitral valve prolapse is common and mitral regurgitation, which may require valve replacement, is the leading cause of cardiovascular morbidity.

Continued on page A47

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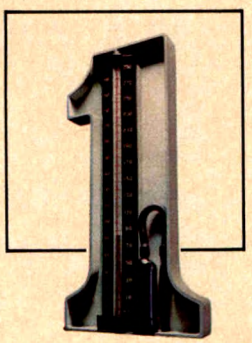

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The starting dose—one 50 mg tablet a day—becomes the long-term maintenance dose for most patients.

Time-consuming dosage adjustments are eliminated and optimal patient compliance is virtually assured.

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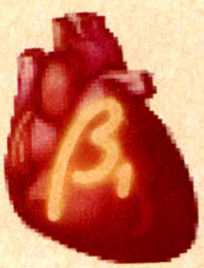

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

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INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m²)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

Reference: 1. Opie LH, Jee L, White D: Antihypertensive effects of nifedipine combined with cardioselective beta-adrenergic receptor antagonism by atenolol. *Am Heart J* 1982; 104:606-612.

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MISCELLANEOUS TOPICS

359 Physical Conditioning and Left Ventricular Performance in the Elderly: Assessment by Radionuclide Angiocardiography

DOUGLAS D. SCHOCKEN, JAMES A. BLUMENTHAL, STEVEN PORT, PAULA HINDLE, and R. EDWARD COLEMAN

To assess the effects of physical training on left ventricular (LV) performance in the elderly, a group of 24 norma elderly persons (mean age 72 years) screened for cardiovascular disease underwent examination of LV functio by rest and exercise radionuclide angiocardiography (RNA) both before and after a 12-week physical condi tioning program. After training, the subjects' functional capacity and double product at a matched submaxima work load had improved significantly. RNA disclosed increased exercise LV end-diastolic volume index and car diac index after the conditioning program. However, both the exercise-induced decrease in LV ejection fractio and concomitant increase in LV end-systolic volume noted before training persisted. These findings suggest tha deconditioning is not a significant contributor to the decline in LV contractile performance seen in the elderly.

365 Abnormal Thallium-201 Scans in Patients With Chest Pain and Angiographically Normal Coronary Arteries

BRUCE C. BERGER, RICHARD ABRAMOWITZ, CHAN H. PARK, ANIL G. DESAI, MARK T. MADSEN, EDWARD K. CHUNG, and ALBERT N. BREST

We reviewed the exercise thallium-201 (T1-201) scans and clinical data in 41 patients with chest pain and nor mal coronary arteries to identify clinical factors associated with false-positive studies. The studies were per formed before angiography and often precipitated referral. Of the 41 patients, 11 (27%) had abnormal exercis T1-201 scans. No clinical factor was significantly associated with a false-positive T1-201 study. Of the 11 pa tients with abnormal scans, 9 had ≥ 1 cardiac abnormality, including mitral valve prolapse, conduction abnor malities and abnormal left ventricular diastolic pressure. Thus, (1) when results of exercise T1-201 imaging ar used to refer patients for angiography, false-positive T1-201 studies are common; (2) clinical factors do not pre dict false-positive T1-201 studies; and (3) patients with chest pain, normal coronary arteries, and abnormal T1 201 scans frequently have other cardiac abnormalities.

371 Natural History of Platelet Deposition on Dacron Aortic Bifurcation Grafts in the First Year After Implantation

JOHN R. STRATTON, BRIAN L. THIELE, and JAMES L. RITCHIE

Indium-111 platelet imaging was performed on 8 men 1 to 2 weeks after Dacron® arterial graft implantation anc in 5 of these patients, at a mean of 31 and 55 weeks. Serial imaging was performed 24 to 96 hours after platele labeling. Quantitative analysis was performed using a graft/blood ratio that compared background-correcte platelet activity in the graft region to whole blood platelet activity. Additionally, blinded qualitative visual analysi of the images compared graft activity with the activity in adjacent native arteries. The mean of all graft/blood ra tios (24, 48, 72, and 96 hours) progressively decreased from 4.4 ± 2.1 (± 1 standard deviation) at 1 to 2 week to 3.0 ± 1.8 at 31 weeks ($p = 0.002$). There was no further decrease at 55 weeks (2.8 ± 2.0). For comparisor 12 normal subjects without grafts had a mean ratio of 1.8 ± 0.7. Visual analysis detected platelet deposition i 7 of 8 grafts at 1 to 2 weeks, 4 of 5 at 31 weeks, and 4 of 5 at 55 weeks. Deposition decreased qualitatively i 2 of 5 patients at late study. It is concluded that there is consistent, early platelet deposition on Dacron grafts i humans. Although deposition decreases over 31 weeks, it remains readily detectable in most patients at 1 yea These findings suggest absent or incomplete endothelialization of the graft flow surface in man in the first yea after implantation.

METHODS

375 Systematic Analysis of Contrast Echocardiograms

RICHARD S. MELTZER, ZVI VERED, JOS ROELANDT, and HENRY N. NEUFELD

Contrast echocardiography was first described in 1968, and many articles since then have described clinical an experimental uses for the technique. It is performed at least occasionally in most echocardiography laborat ries. However, most physicians use this technique merely to obtain a "yes-no" answer with respect to the pres ence of a shunt or, more rarely, structure identification. Much more information is potentially available tha merely yes or no. This report reviews some of the different types of information available from contrast echoca diographic records (timing of contrast appearance within the cardiac cycle, relative timing of appearance in di ferent cardiac structures, relative intensity of contrast opacification, cyclic changes in contrast opacificatio negative contrast effect, slope of contrast trajectories on M-mode contrast echocardiography and clearanc times).

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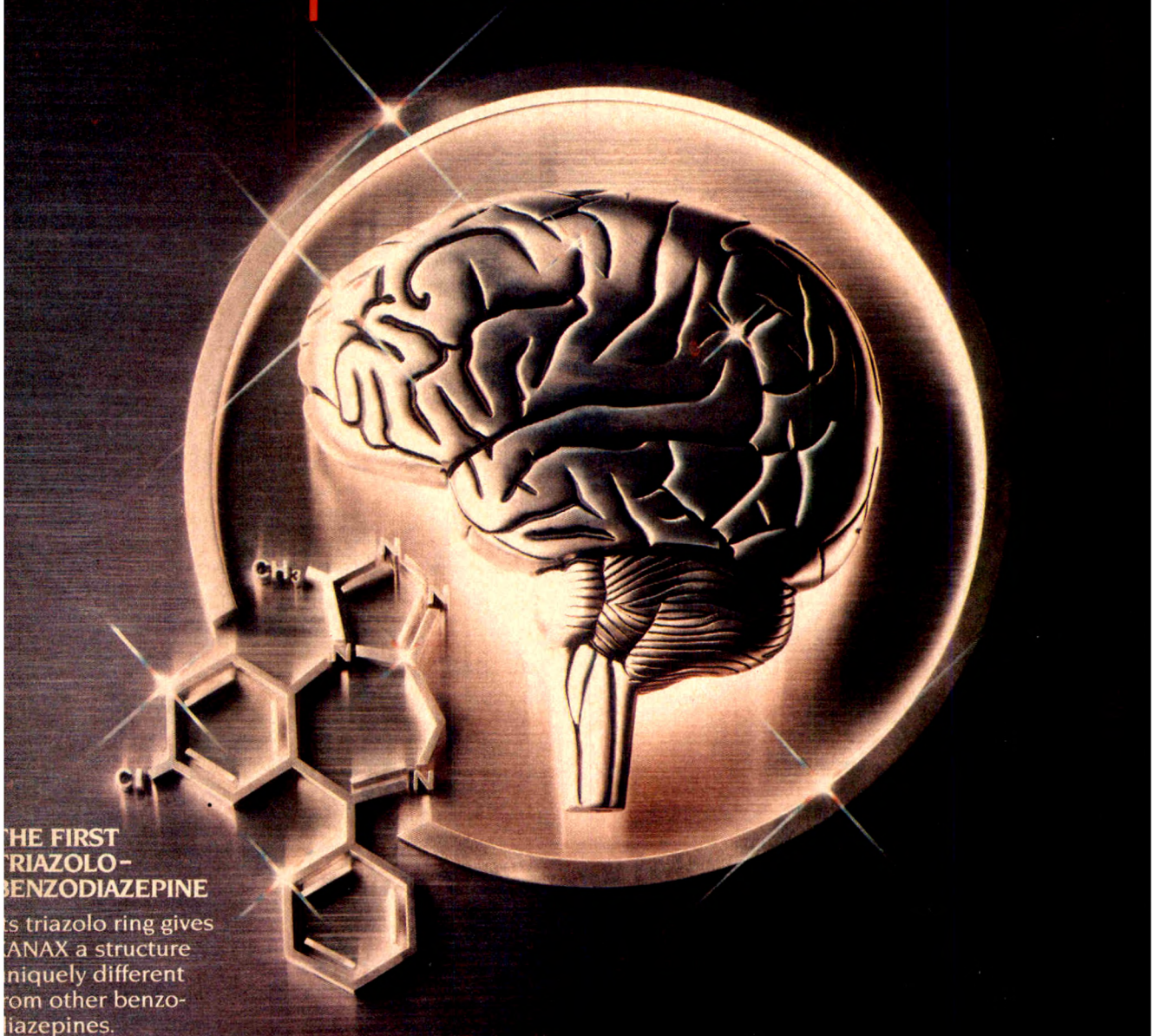

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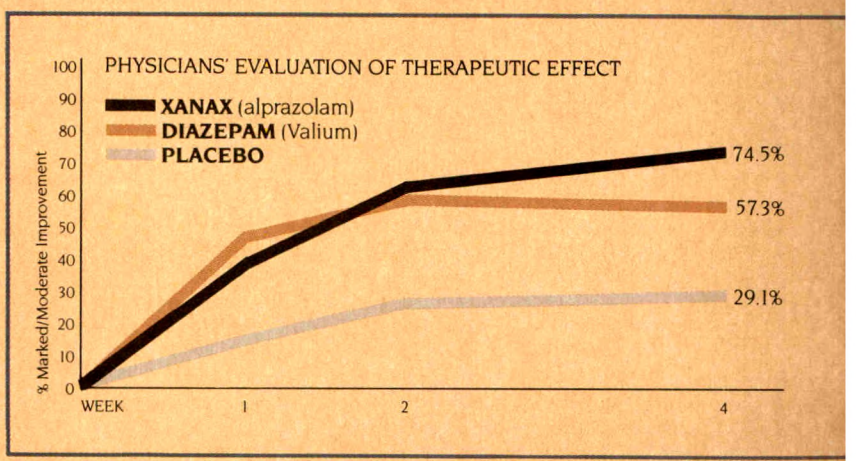
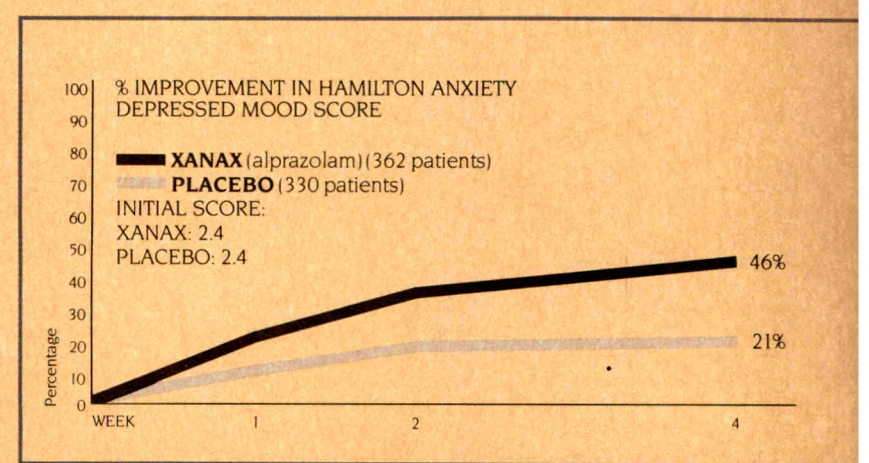


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE: XANAX 0.25–0.5 mg T.I.D.

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Please see next page for brief summary of prescribing information.

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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J Clin Psychiatry 42 (9):347-351, 1981.

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381 Left Atrial Abnormality As an Electrocardiographic Criterion for the Diagnosis of Left Ventricular Hypertrophy in the Presence of Right Bundle Branch Block

MARVIN L. MURPHY, NIHAL THENABADU, NEIL de SOYZA, JAMES E. DOHERTY, and BONNIE J. BAKER

Left atrial (LA) abnormality determined from precordial lead V_1 was assessed by 2 observers as a criterion of left ventricular (LV) hypertrophy in the presence of right bundle branch block (BBB) in 23 patients. The presence of LV hypertrophy was confirmed from a postmortem cardiac partition technique and defined at 2 levels of confidence: probable and definite hypertrophy. The 2 observers differentiated between the hypertrophied and normal-sized ventricle in most instances in the presence of right BBB by using LA abnormality as an electrocardiographic criterion. Observer performance of recognition of LA abnormality in this study was satisfactory, with 91% agreement between observers. Our results are comparable and, in some instances, superior to other criteria commonly recommended to diagnose LV hypertrophy on the electrocardiogram without right BBB.

384 Automatic Computer Processing of Digital 2-Dimensional Echocardiograms

ANDREW J. BUDA, EDWARD J. DELP, CHARLES R. MEYER, JANICE M. JENKINS, DAVID N. SMITH, FRED L. BOOKSTEIN, and BERTRAM PITT

The development of automatic computerized methods should improve the ability to extract quantitative data from 2-dimensional echocardiographic studies and improve the reliability of these data. A method of direct digital acquisition that improves signal-to-noise ratio, and thus improves endocardial and epicardial border definition has been developed. Using edge detection algorithms, it has been possible to automatically define anatomically appropriate endocardial and epicardial borders. Subsequent left ventricular regional and global analysis can be performed quantitatively frame by frame. These technologic improvements in 2-dimensional echocardiographic data acquisition and processing should facilitate quantitative studies in the analysis of left ventricular function.

EXPERIMENTAL STUDIES

390 Early Degradation of Collagen After Acute Myocardial Infarction in the Rat

RICHARD O. CANNON, III, JAGDISH W. BUTANY, BRUCE M. McMANUS, EDITH SPEIR, ALAN B. KRAVITZ, ROBERTO BOLLI, and VICTOR J. FERRANS

Collagen, which forms a structural fibroskeleton in healthy myocardium, was measured in infarct tissue from control rats at 24 hours after coronary artery ligation, and rats made leukopenic by prior whole-body irradiation (white blood cell count $<300/mm^3$). Control rats had a 25% decrease in myocardial hydroxyproline content compared with unoperated rats, associated histologically with an influx of inflammatory cells at the infarct margins. There was no significant collagen degradation in leukopenic rats. Electron microscopic studies revealed greater preservation of collagen in the 24-hour-old infarcts of leukopenic rats than in those of controls. These results suggest that there is early collagen degradation after myocardial infarction, which is mediated by inflammatory cells and may be of pathogenetic importance in the development of cardiac rupture and aneurysm formation.

396 Assessment of Quantitative Methods for 2-Dimensional Echocardiography

HORACE L. WYATT, ROBERTO V. HAENDCHEN, SAMUEL MEERBAUM, and ELIOT CORDAY

Several 2-dimensional echocardiographic (2-DE) methods were tested in vitro for accuracy of linear and cross-sectional measurements and in vivo for left ventricular (LV) volume reconstruction. With echocardiographic low and high gains and with precise in vitro calibrations, we studied myocardial slice thickness measured by leading-trailing, trailing-leading, and leading-leading methods. Regression analysis of echocardiographic versus direct measurements yielded excellent correlations for all 3 methods, with an interobserver variability of <3%. Accuracy of measurement was satisfactory only for the leading-leading method. Thin myocardial slices were applied to cylinders and fixed in formalin to produce precise cavity areas. Regression analysis of echocardiographic versus actual cavity area gave high correlations, and low interobserver variability for both inner and leading edge methods, but leading edge was most accurate. Although in vivo 2-DE echocardiography in dogs underestimated angiographic volumes, generally good correlations were obtained. The leading edge method showed the least underestimation. Thus, for 2-DE, the leading edge method is most accurate for linear and cross-sectional measurements of myocardium and for application to LV volumes.

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P. H. NATH, BENIGNO SOTO, JOHN H. HOLT, and LOWELL F. SATLER

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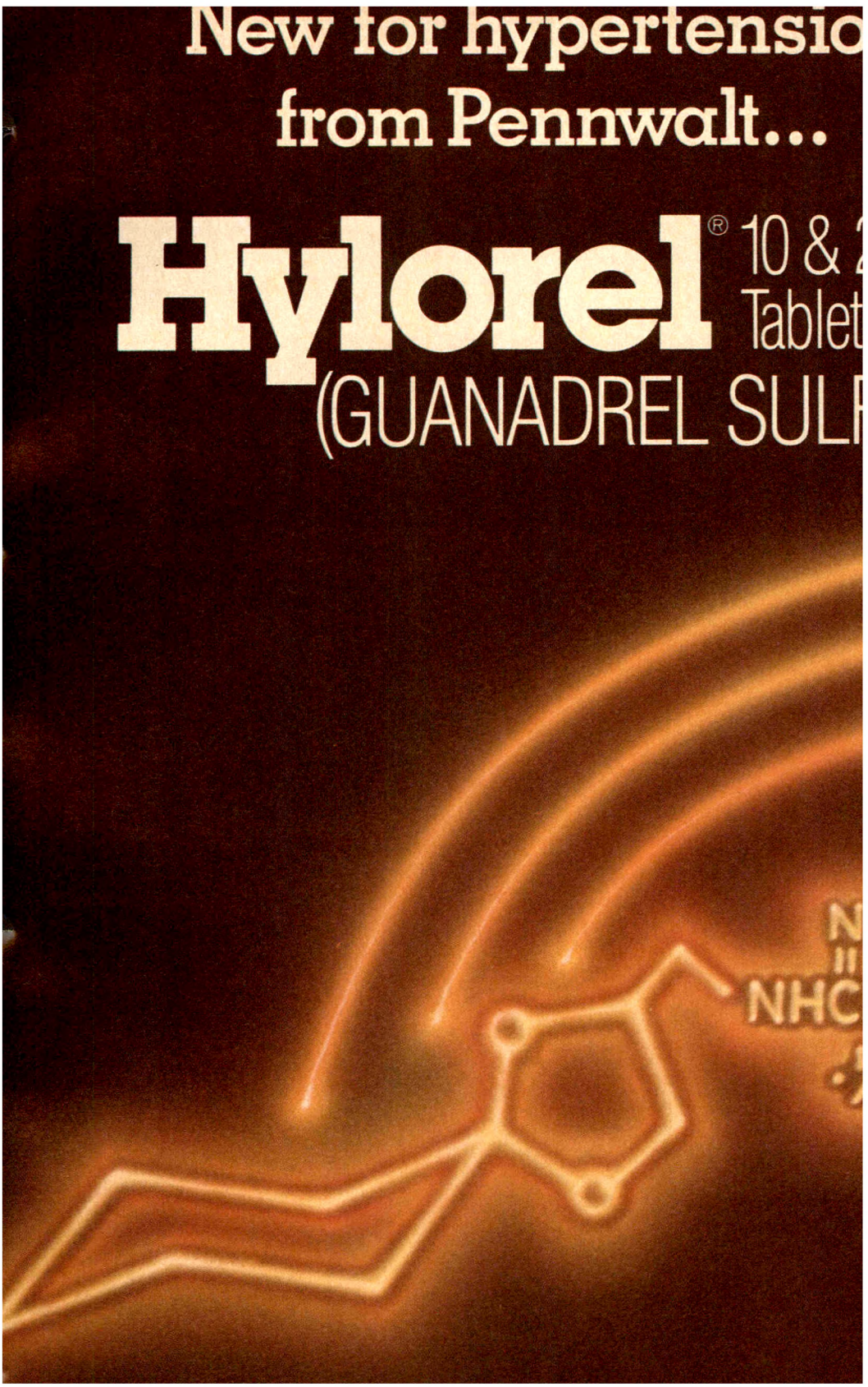
New for hypertensio
from Pennwalt...
Hylorel® 10 & 2
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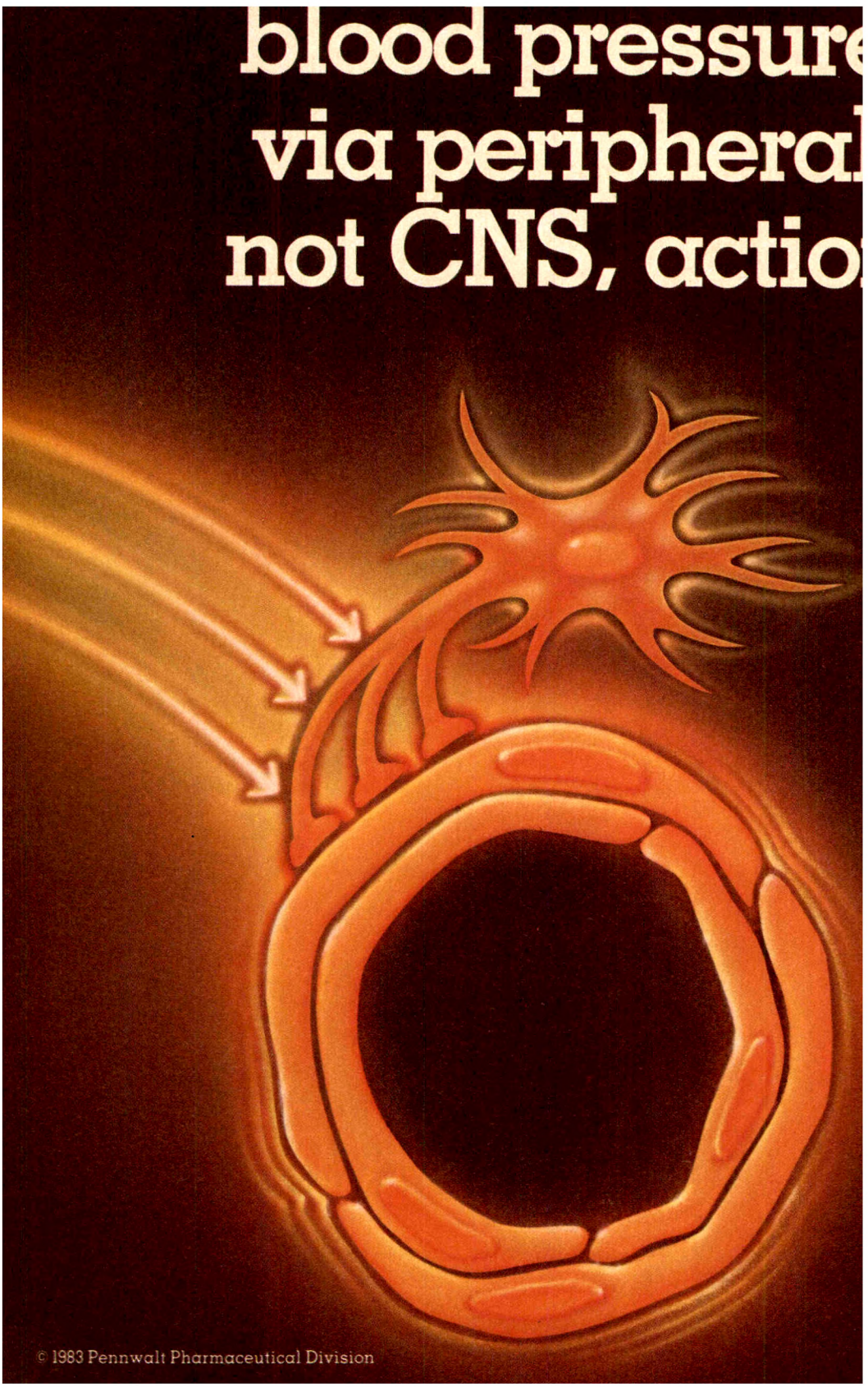
blood pressure
via peripheral
not CNS, actio
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HYLOREL: A New Peripheral Sympathetic Inhibitor

HYLOREL controls blood pressure via peripheral, not CNS, action... allowing relaxation of the arterioles. Some CNS effects have been reported in patients treated with antihypertensive regimens that included HYLOREL. With a diuretic, HYLOREL is useful in the Step-2 treatment of hypertension.

HYLOREL is a well-tolerated alternative to beta blockers, prazosin, and centrally acting antihypertensives, when a diuretic alone is not enough.

As Effective as Aldomet®*[1]

HYLOREL, in controlled clinical studies, provided blood pressure control comparable to Aldomet, with less drowsiness, depression, and impotence. Patients treated with Aldomet had less diarrhea and fewer orthostatic effects than did those treated with HYLOREL Tablets (guanadrel sulfate).[1]

Orthostatic hypotension, diarrhea, and ejaculation disturbances may occur in patients but seldom have been a cause for discontinuing HYLOREL therapy (see Table 1).

Table 1.
Percent of Patients Discontinuing Therapy

	HYLOREL	Methyldopa	Guanethidine
orthostatic faintness	0.6	0.7	6.0*
syncope	0.4	0.3	2.0
other faintness	1.2	0.0	0.0
increased bowel movements	0.8	0.7	1.4
drowsiness	0.0	1.9*	0.0
fatigue	0.2	2.6*	0.0
ejaculation disturbances	0.4	0.0	0.0
Number of patients analyzed	(481)	(271)	(222)

*Significantly greater than HYLOREL ($p<0.003$).

A Well-tolerated and Useful Choice for Step-2 Treatment of Hypertension

HYLOREL, with a diuretic, is easy to use and economical... for the Step-2 treatment of hypertension.

HYLOREL has not caused a significant change in cardiac output nor adverse effects on liver function.

HYLOREL should not be used in patients with pheochromocytoma nor concurrently with monoamine oxidase inhibitors. HYLOREL should not be given to patients with frank congestive heart failure.

HYLOREL is not contraindicated in patients with ischemic heart disease or peripheral vascular disease.

Two Doses a Day for Most Patients With Hypertension

HYLOREL is prompt acting and rapidly cleared. The dosage can be conveniently titrated. Two doses per day adequately control blood pressure for 24 hours and are associated with minimal morning orthostatic hypotension. Dosage may be adjusted weekly or monthly to fit the patient's needs.

HYLOREL is a Step-2 therapy and should be added to a diuretic regimen for optimal blood pressure control. HYLOREL should be given in divided doses... the usual starting dose is 10 mg per day. The dosage range for most patients is 20 to 70 mg per day.

*Aldomet® is a registered trademark of Merck Sharp & Dohme.

1. Nugent CA, Palmer JD, Ursprung JJ: Guanadrel sulfate compared with methyldopa for mild and moderate hypertension. *Pharmacotherapy* 2:378-383, 1982.

New for hypertension from Pennwalt

Hylorel® 10 & 25 mg Tablets (GUANADREL SULFATE)

Please refer to the brief summary, including Warnings and Adverse Reactions, on the following page.

Hylorel® 10 & 25 mg Tablets
(GUANADREL SULFATE)

Before prescribing see complete prescribing information; a brief summary follows.

DESCRIPTION: HYLOREL Tablets contain guanadrel sulfate—an antihypertensive agent belonging to the class of adrenergic neuron inhibitors.

CLINICAL PHARMACOLOGY: Guanadrel sulfate is an orally effective antihypertensive agent that lowers both systolic and diastolic arterial blood pressures. Guanadrel sulfate inhibits sympathetic vasoconstriction by inhibiting norepinephrine release from neuronal storage sites and also causes depletion of norepinephrine from nerve endings. This results in relaxation of vascular smooth muscle. No significant change in cardiac output accompanies the blood pressure decline in normal individuals.

INDICATIONS AND USAGE: HYLOREL is indicated for the treatment of hypertension in patients not responding adequately to a thiazide-type diuretic. HYLOREL is Step-2 therapy and should be added to a diuretic regimen for optimum blood pressure control.

CONTRAINDICATIONS: Known or suspected pheochromocytoma; concurrently or within one week of the use of monoamine oxidase inhibitors; patients hypersensitive to the drug; patients with frank congestive heart failure.

WARNINGS: Orthostatic Hypotension and its consequences (dizziness and weakness) are frequent in people treated with HYLOREL. Rarely, fainting upon standing or exercise is seen. Patients with known regional vascular disease (cerebral, coronary) are at particular risk from marked orthostatic hypotension, and HYLOREL should be avoided in them unless drugs with lesser degrees of orthostatic hypotension are ineffective or unacceptable.
Surgery—HYLOREL should be discontinued 48–72 hours before elective surgery to reduce the possibility of vascular collapse during anesthesia. If emergency surgery is required, the anesthesiologist should be made aware that the patient has been taking HYLOREL, and that preanesthetic and anesthetic agents should be administered cautiously in reduced dosage. If vasopressors are needed, they must be used cautiously, as guanadrel can enhance the pressor response to such agents and increase their arrhythmogenicity.
Drug Interactions—Tricyclic antidepressants and indirect-acting sympathomimetics can reverse the effects of neuronal blocking agents. IN VIEW OF THE PRESENCE OF SYMPATHOMIMETIC AMINES IN MANY NON-PRESCRIPTION DRUGS FOR THE TREATMENT OF COLDS, ALLERGY, OR ASTHMA, PATIENTS GIVEN GUANADREL SHOULD BE SPECIFICALLY WARNED NOT TO USE SUCH PREPARATIONS WITHOUT THEIR PHYSICIAN'S ADVICE. Drugs that affect the adrenergic response by the same mechanisms as guanadrel sulfate or by other mechanisms would be expected to potentiate the effects of HYLOREL causing excessive postural hypotension and bradycardia. These include alpha or beta adrenergic blocking agents and reserpine. There is no clinical experience with such combinations.
Asthmatic patients with bronchial asthma: need special attention as their condition may be aggravated by catecholamine depletion and sympathomimetic amines may interfere with the hypotensive effect of guanadrel.

PRECAUTIONS: General—Salt and water retention may occur. In clinical studies, major problems did not arise because of concomitant diuretic use. Patients with heart failure and patients with renal failure have not been studied on HYLOREL. HYLOREL should be used cautiously in patients with a history of peptic ulcer.
Carcinogenesis—No evidence of carcinogenic potential appeared in animal studies.
Mutagenesis—Salmonella testing showed no evidence of activity.
Pregnancy Category B
Impairment of fertility and teratogenic effects—Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to HYLOREL. There are no adequate and well-controlled studies in pregnant women. HYLOREL should be used in pregnant women only when the potential benefit outweighs the potential risk to mother and infant.
Nursing mothers—It is not known whether or not guanadrel sulfate is excreted in human milk.
Pediatric Use—Safety and effectiveness of guanadrel in children have not been established.

ADVERSE REACTIONS: The adverse reaction data in this section are derived principally from comparative long-term studies with methyldopa and guanethidine. Side effects were assessed through the use of periodic questionnaires, a method that tends to give high adverse reaction rates. Reasons for discontinuation of therapy are shown in the following table.

PERCENT OF PATIENTS WHO DISCONTINUED THERAPY

	Guanadrel	Methyldopa	Guanethidine
Orthostatic faintness	0.6	0.7	6.0
Syncope	0.4	0.3	2.0
Other faintness	1.2	0.0	0.0
Increased bowel movements	0.8	0.7	1.4
Drowsiness	0.0	1.9	0.0
Fatigue	0.2	2.6	0.0
Ejaculation disturbances	0.4	0.0	0.0

The following percentages represent the number of patients who reported an event at least once over the treatment periods (6 months to 3 years). For such long-term studies, these rates for side effects, often found in untreated people as well as in association with adrenergic neuron blocking agents, tend to be high and accumulate with time. The rates for methyldopa and guanethidine should aid in interpretation of this information. It can be seen that serious consequences of the orthostatic effect of guanadrel, such as syncope were very uncommon.

1544 guanadrel, 330 guanethidine and 743 methyldopa patients were evaluated in comparison studies. The observed incidence rates of major drug-related side effects for guanadrel, guanethidine and methyldopa respectively are as follows: Orthostatic faintness: 49%, 48%, 41%; other faintness: 47%, 45%, 46%; increased bowel movements: 31%, 36%, 28%; ejaculation disturbances:18%, 22%, 21%; impotence: 5.1%, 7.2%, 12.2%; syncope: 0.4%, 2%, 0.3%; urine retention: 0.2%, 0%, 0%. Apart from these adverse effects, many others were reported. Relationship to therapy is less clear, although some (such as peripheral edema with all three drugs, depression with methyldopa) are in part drug related. All adverse effects reported in at least 1% of guanadrel patients are listed in the full prescribing information. (This is a brief summary.)

DOSAGE AND ADMINISTRATION: As with other sympathetic suppressant drugs, the dose response to HYLOREL varies widely and must be adjusted for each patient until the therapeutic goal is achieved. With long-term therapy, some tolerance may occur and the dosage may have to be increased.
Because HYLOREL has a substantial orthostatic effect, monitoring both supine and standing pressure is essential, especially while dosage is being adjusted.
HYLOREL should be administered in divided doses. The usual starting dosage for treating hypertension is 10 mg per day, which can be given as 5 mg b.i.d. by breaking the 10 mg tablet. Because the half-life is approximately ten hours, the dosage should be adjusted weekly or monthly until blood pressure is controlled. Most patients will require daily dosage of the range of 20 to 75 mg usually in twice daily doses. For larger doses 3 or 4 times daily dosing may be needed.

COMBINATION THERAPY: HYLOREL has not been studied in combination with antihypertensive drugs other than thiazide diuretics.

HOW SUPPLIED: HYLOREL Tablets (guanadrel sulfate) are available as follows:
10 mg, scored elliptical tablets (light orange)
Bottles of 100 NDC 0018-0787-71
25 mg, scored elliptical tablets (white)
Bottles of 100 NDC 0018-0788-71

Caution: Federal law prohibits dispensing without a prescription.

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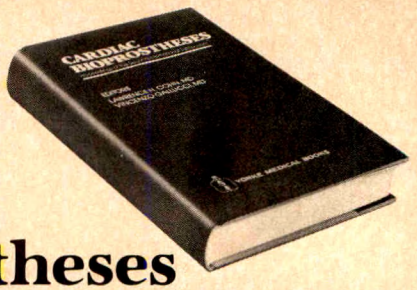

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

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If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

Who are the editors?

Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

• Section 1 CLINICAL ANALYSIS • Section 2 HEMODYNAMICS • Section 3 THROMBOEMBOLISM • Section 4 PEDIATRIC VALVE REPLACEMENT • Section 5 EXPERIMENTAL PATHOLOGY • Section 6 EXPLANT PATHOLOGY • Section 7 BIOPROSTHETIC BIOENGINEERING • Section 8 LONG-TERM FOLLOW-UP • Section 9 SUMMING UP • AUTHOR INDEX • SUBJECT INDEX

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The medical literature describes currently accepted indications and contraindications for the various pacing/sensing modes. However, the physician's clinical experience and judgment must ultimately determine the pacing mode best suited to the patient's needs.

When spontaneous beats are expected, a sensing mode (inhibited or triggered) is indicated. *Asynchronous pacing is contraindicated for long-term pacing when inherent activity is present or likely to be present in the chamber being paced.*

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Atrial-synchronized ventricular pacing (VVD or VAT) and dual-chamber pacing (DVI or DDD) are indicated for patients who would benefit from restoration of atrial contribution to cardiac output and the control of heart rate. Atrial-synchronized ventricular pacing is indicated for patients with permanent heart block and normal atrial rhythm. Dual-chamber pacing is indicated for A-V conduction disturbances with sinus node dysfunction (sinus bradycardia with A-V block, bradytachy syndrome). *Atrial-synchronized ventricular pacing and automatic dual-chamber demand pacing modes are contraindicated in the presence of persistent atrial flutter or atrial fibrillation.* The VVI mode is recommended for these conditions.

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Precautions

Cordis implantable pacers may respond to programmers of other manufacturers. Because of the unknown nature of such response, use only the Cordis Model 255A Programmer III for reprogramming.

Use pacers on a first-in, first-out basis prior to the "Use before" date on the package.

Warnings

None

Adverse Effects

A number of complications related to pacer therapy have been reported in the medical literature. The complications listed below may occur at any time after implantation.

Pacer – battery depletion, electromagnetic interference, component malfunction, decreased sensitivity.

Lead – unsatisfactory electrode position, fracture, displacement, perforation of heart wall, faulty connection with pacer, migration through body tissue.

Patient – reaction, infection/erosion, increase in stimulation threshold, embolism, thrombosis.

Caution: Federal (U.S.A.) law restricts these devices to sale by or on the order of a physician.

Prior to use, refer to the *Instructions for Use* for more information.

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NITRODISC™

(NITROGLYCERIN)

5 mg/24 hr
10 mg/24 hr discs

DESCRIPTION: Nitrodisc incorporates a patented Microseal Drug Delivery™ system consisting of a solid, nitroglycerin-impregnated polymer bonded to a flexible, non-sensitizing adhesive bandage. It is designed to be applied topically. Nitrodisc provides constant and controlled drug delivery over a uniform skin surface area for 24 hours.

Nitrodisc is available in two strengths which release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system contains 16 mg nitroglycerin over an 8 cm^2 releasing surface. The 10 mg/24 hr system contains 32 mg nitroglycerin over a 16 cm^2 releasing surface.

INDICATIONS AND USAGE: Nitrodisc is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Nitrodisc (nitroglycerin) is contraindicated in patients known to be intolerant of organic nitrate drugs, and in patients with marked anemia, increased intraocular pressure, or increased intracranial pressure.

WARNINGS: In patients with acute myocardial infarction or congestive heart failure, Nitrodisc should be used under careful clinical and/or hemodynamic monitoring.

In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent potential withdrawal reactions, which are characteristic of all vasodilators in the nitrate class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitrodisc is not intended for immediate relief of anginal attacks. For this purpose, occasional use of sublingual preparations may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Nitrodisc therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, Nitrodisc (nitroglycerin) dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION: Nitrodisc should be applied once each day. To use Nitrodisc, follow the instructions on the package. Nitrodisc should be applied to an intact skin site free of hair and not subject to excessive movement. It should not be applied to the distal parts of the extremities. A suitable area should be shaved free of hair, if necessary. The application site should be changed slightly each time to avoid undue skin irritation. A new Nitrodisc should be applied if the product loosens.

The optimal dosage regimen should be selected based upon the clinical response, the side effects, and the effects of therapy upon blood pressure and heart rate. It is recommended that therapy be initiated with the smaller Nitrodisc, and that the larger Nitrodisc be utilized when a greater response is desired. In the event that higher doses are necessary, multiple pads may be applied.

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3C2

Nitrodisc™
(nitroglycerin)
5mg/24hr
5 mg/24 hr 10 mg/24 hr discs
NITRODISC™
(NITROGLYCERIN)
SEARLE
Contraindications for nitroglycerin include increased intraocular pressure. Side effects include headache, hypotension, flushing, and dizziness. In terminating treatment, both the dosage
Please see the preceding page for a brief summary

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The American Journal of CARDIOLOGY

VOLUME 5

NUMBER

CORONARY HEART DISEASE

Coronary Reperfusion and Bezold-Jarisch Reflex (Bradycardia and Hypotension)

PAOLO ESENTE, MD, ALESSANDRO GIAMBARTOLOMEI, MD, GOFFREDO G. GENSINI, MD, and CARLOS DATOR, MD

This study reports the occurrence of bradycardia and hypotension (Bezold-Jarisch reflex) induced by myocardial reperfusion. Among 92 patients undergoing interventional catheterization for intracoronary thrombolysis in an early phase of acute myocardial infarction, left anterior descending, right coronary, and left circumflex (LC) arteries were identified as the "infarct vessel" in 44, 41, and 7 cases, respectively. The Bezold-Jarisch reflex occurred in 15 of 23 patients (65%) after right coronary recanalization and in 1 of 34 patients after left anterior descending recanalization. The reflex also was observed in 4 (22%) of 18 patients with nonoccluded or nonrecanalized right coronary arteries. The average time from onset of symptoms to righ recanalization was significantly shorter ($p < 0.01$) among patients in whom the reflex did not develop Atropine, postural changes, or temporary pacing, o all 3, were generally sufficient to control symptoms The findings of this study are substantially paralle to those reported by others and confirm that reper fusion of the inferoposterior myocardium is capable of stimulating a cardioinhibitory reflex. Follow-up data available in 15 patients with occluded and re canalized right coronary arteries indicate that the occurrence of the Bezold-Jarisch reflex after re perfusion is not a reliable predictor of myocardia salvage.

The Bezold-Jarisch reflex, an inhibitory reflex characterized by bradycardia and hypotension, is induced by stimulation of receptors situated in the left ventricle.[1,2] These receptors signal in nonmyelinated vagal afferent fibers and respond to chemical, mechanical, or metabolic stimuli.[3–5] In the cat, increased discharge from left ventricular receptors was noted after coronary occlusion as well as reperfusion.[5]

Ischemia-activated vagal afferent receptors are located primarily in the inferoposterior wall of the canine heart.[6] The exact location of similar receptors in man has not been determined experimentally. However, th high incidence of bradycardia-hypotension syndrom observed during the early phase of inferior myocardia infarction[7] strongly suggests that in the human heart such receptors are situated in the inferoposterior lef ventricular wall. This study reports the occurrence o the Bezold-Jarisch reflex induced by myocardial re perfusion in man.

Methods

From May 1981 through December 1982, 92 patients un derwent cardiac catheterization, coronary angiography, an intracoronary streptokinase infusion during the early hour of an evolving acute myocardial infarction. The procedur started <6 hours from the onset of symptoms in 84 patients At the inception of catheterization, all patients had unequiv ocal electrocardiographic evidence of acute injury and all bu 1 had chest pain. Cardiogenic shock was present in 4 pa tients.

From the Msgr. Toomey Cardiovascular Laboratory, St. Joseph's Hospital Health Center, Syracuse, New York. Manuscript received March 18, 1983, accepted May 10, 1983.

Address for reprints: Paolo Esente, MD, Msgr. Toomey Cardiovascular Laboratory, St. Joseph's Hospital Health Center, 301 Prospect Avenue, Syracuse, New York 13203.

TABLE I Settings of the Bezold-Jarisch Reflex

	Infarct Vessel		
	LAD (44 pts)	RCA (41 pts)	Cx (7 pts)
Recanalized	34	23	4
Bezold-Jarisch reflex	1(3%)	15(65%)	0
Not recanalized	6	9	3
Bezold-Jarisch reflex	0	2(22%)	0
Not occluded	4	9	0
Bezold-Jarisch reflex	0	2(22%)	. . .

Cx = left circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery.

All patients were premedicated with hydrocortisone, diphenhydramine, and morphine sulfate as required. After a bolus of 50 to 100 mg, lidocaine was infused at a rate of 2 to 4 mg/min. Nonhypotensive patients received nitroglycerin at a rate of 15 to 120 μg/min. The Sones technique was used in all cases. Intracoronary nitroglycerin, 0.4 mg bolus, was injected into the "infarct" vessel (that is, the obstructed or occluded branch supplying the infarcted area) followed by a streptokinase bolus of 10,000 U and constant streptokinase infusion at 4,000 U/min through a pressurized drip. Control visualization of the "infarct" vessel was obtained at 5- to 15-minute intervals or when rhythm changes were noted. Leads III and V_5 were monitored in anterior infarctions, leads I and III in inferior infarctions.

Results

Arteriographic findings: Left anterior descending (LAD), right coronary, and left circumflex (LC) coronary arteries were identified as the "infarct" vessel in 44, 41, and 7 cases, respectively. The "infarct" vessel was not occluded in 13 patients (4 LAD and 9 right coronary arteries).

Intracoronary thrombolysis: Recanalization of occluded coronary arteries was achieved in 34 of 40 LAD, in 23 of 32 right coronary, and in 4 of 7 LC arteries. The average recanalization time from the onset of symptoms was 215 minutes.

Bezold-Jarisch reflex: Hypotension and bradycardia (either sinus or secondary to atrioventricular block) occurred in 20 patients (22%). The settings in which the Bezold-Jarisch reflex was noted are summarized in Table I; it is noteworthy that in 19 of 20 times it was associated with involvement of the right coronary artery.

Patients with an occluded and recanalized coronary artery developed hypotension and bradycardia immediately after restoration of flow. When the Bezold-Jarisch reflex occurred in patients who were not recanalized or did not have an occluded "infarct" vessel, it was not associated with any particular event.

The only occurrence of Bezold-Jarisch reflex associated with LAD recanalization was observed in a patient whose LAD artery was the source of collateral blood flow to an occluded right coronary artery. In 1 patient without hypotension and bradycardia after right coronary artery recanalization, the occlusion was located distal to the origin of the posterior descending artery. None of the occluded LC arteries was of the "dominant" type.

FIGURE 1. Right coronary artery in the left anterior oblique projection showing mid-segment occlusion with an upward convexity crescent configuration.

The average time from onset of symptoms to right coronary artery recanalization was 240 minutes (range 160 to 324) among patients in whom hypotension and bradycardia developed and 195 minutes (range 125 to 236) among patients in whom they did not ($p < 0.01$.)

Three patients with recanalized right coronary arteries had had previous myocardial infarction of the inferior wall; recanalization-induced hypotension and bradycardia occurred in 2. Postural changes, atropine sulfate, or temporary pacing was used in all patients in whom hypotension and bradycardia developed. Only 1 patient required additional pharmacologic intervention.

Representative case: A 72-year-old man without a history of ischemic heart disease experienced severe retrosternal pain at 8:00 A.M. on November 7, 1982. An electrocardiogram taken at 10:30 A.M. in the emergency room showed an injury pattern in inferior leads with reciprocal changes in lateral and precordial leads. A diagnosis of acute inferior wall infarction was made and the patient was transferred to our institution for intracoronary thrombolysis. Left ventricular pressure was

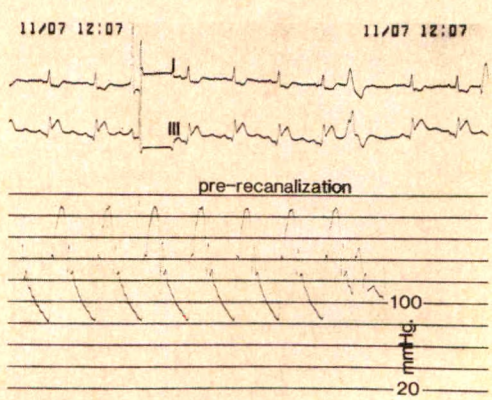

FIGURE 2. Leads I (**top**) and III; aortic pressure before recanalization.

190/26 mm Hg. Coronary arteriography revealed moderate stenosis of the LAD and LC arteries and occlusion of the right (Fig. 1). Intracoronary streptokinase infusion was started at 12:01. At 12:07, the heart rate was 75 beats/min and aortic pressure 188/82 mm Hg (Fig. 2). A sudden decrease in heart rate and aortic pressure was noted at 12:13. Contrast material was promptly injected into the right coronary artery (Fig. 3) and the occurrence of recanalization established. At 12:14 (Fig. 4), the heart rate was 54 beats/min and the aortic pressure 77/40 mm Hg. Pallor and diaphoresis were noted. Elevation of lower extremities and injection of atropine sulfate, 0.5 mg, resulted in rapid normalization. The left ventriculogram taken at the end of the procedure showed inferoposterior akinesia, with an ejection fraction of 46%. Creatine phosphokinase peaked at 865 U, lactic dehydrogenase at 241 U, and serum glutamic oxalacetic transaminase at 177 U.

Discussion

Arrhythmias associated with intracoronary thrombolysis have been reported.[8,9] The occurrence of hypotension and bradycardia after right coronary recanalization has been described recently.[10,11] Our findings are substantially parallel to those reported by Goldberg et al[10] and Wei et al,[11] particularly the close temporal relation between reperfusion of the inferoposterior left ventricular wall and clinical manifestations of the Bezold-Jarisch reflex, and confirm that myocardial reperfusion is capable of stimulating a cardiac inhibitory reflex.

Stretching due to systolic bulging of ischemic myocardium has been advocated as a possible mechanism of receptor activation.[1] However, systolic bulging of the inferoposterior left ventricular wall was never observed among the patients described in this study. Therefore, it appears that a metabolic rather than a mechanical factor initiates the Bezold-Jarisch reflex.

In this series, the Bezold-Jarisch reflex was never induced by reperfusion of the anterolateral left ventricular wall (except as described in the Results section) whereas its incidence in relation to inferoposterior reperfusion was unquestionably high. This observation confirms that in the human heart, vagal afferent receptors have an inferoposterior distribution.

Parasympathetic overactivity resulting in bradycardia or hypotension, or both, was noted in 55% of patients seen within 30 minutes of the onset of inferior wall myocardial infarction.[7] Our numerically comparable group exhibited a similar incidence after right coronary recanalization, suggesting that interruption and restoration of blood flow to the inferoposterior wall have a substantially identical effect on vagal afferent receptors.

Few patients with a nonoccluded or nonrecanalized right coronary artery developed the Bezold-Jarisch reflex. In these cases, the vagal afferent receptors might have been stimulated by changes in myocardial blood flow undetectable by arteriographic technique (possibly induced by nitroglycerin) or by contrast material.[12] Spontaneous fluctuation in discharge rate of the myocardial vagal afferent receptors was observed in the cat during prolonged ischemia.[5] A similar mechanism could conceivably operate in human subjects.

Clinical Implications

Adequate follow-up data were available in 15 patients 1 to 12 weeks after successful right coronary recanalization. Among 10 patients in whom the Bezold-Jarisch reflex developed, the pattern of inferoposterior wall contraction improved significantly in 6. Of 5 patients in whom the reflex did not develop, 3 improved. Thus recovery of left ventricular function took place in an equal percentage of patients.

If the reperfusion-induced Bezold-Jarisch reflex were to correlate with myocardial salvage, this reflex should occur with greater frequency in situations that favor a greater reduction in infarct size such as a shorter time from the onset of symptoms to recanalization. The opposite was true in our patients; that is, patients who did not manifest the reflex were among those with the shortest intervals between the onset of symptoms and recanalization. Therefore, these observations suggest that the occurrence of the Bezold-Jarisch reflex after

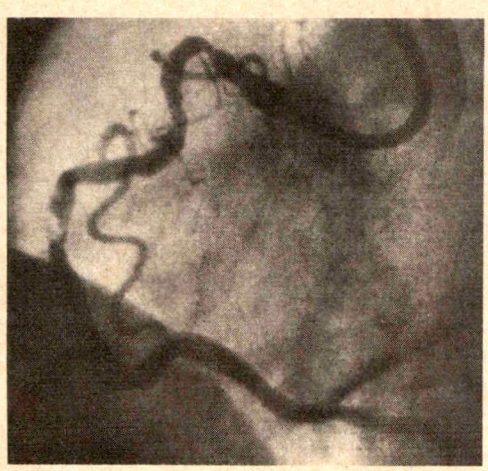

FIGURE 3. Right coronary artery in the left anterior oblique projection showing initial recanalization, but flow to posterior descending and distal right coronary artery is still minimal.

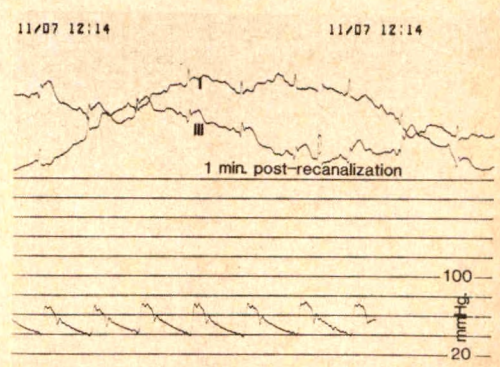

FIGURE 4. Leads I and III 1 minute after recanalization.

coronary reperfusion is not a reliable predictor of myocardial salvage.

Recently, Wei et al[13] theorized that because a reperfusion-induced cardioinhibitory reflex requires viable receptors, the adjacent myocardium is likely to be viable as well; thus, such reflex should herald myocardial salvage. Our results did not support this view, which we share conceptually. Events in the interval between evaluations of left ventricular function could conceivably have affected the extent of myocardial salvage. Further studies on this subject are needed. Because hypotension and bradycardia induced through a vagal reflex occur frequently after right coronary recanalization, it is advisable to administer atropine prophylactically to susceptible patients.

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Natural History of Patients With Single-Vessel Disease Suitable for Percutaneous Transluminal Coronary Angioplasty

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To permit comparison of percutaneous transluminal coronary angioplasty (PTCA) with conventional therapy, the clinical outcome was established in patients who would have been suitable candidates for PTCA but who presented before the technique was available. Coronary angiograms were reviewed of patients who met the following criteria: single-vessel disease with proximal subtotal coronary stenosis, chest pain of at least class II, and cardiac catheterization before 1981. Angiograms were evaluated according to established criteria for PTCA by an experienced angiographer. One hundred ten patients (2.1% of the patient population) were judged suitable for PTCA. Clinical and catheterization findings closely resembled those of patients in the national PTCA registry. Five years after catheterization, 97% of PTCA candidates treated medically were alive and 85% had not had myocardial infarction. Forty-six patients had coronary arter bypass surgery within 6 months of catheterizatio and 10 other patients had subsequent surgery. Fiv years after surgery, 91% were alive and 87% ha not had myocardial infarction. At 6 months of fo low-up, 78% of all patients had improved at leas 1 functional class, and 86% of all patients workin before catheterization were still employed. Func tional capacity was well maintained during long term follow-up (median 6.5 years, range 1.4 t 12.2).

These data indicate that PTCA candidates hav an excellent prognosis for survival, a low risk of in farction, and well-maintained functional capacit when revascularization is reserved for those wit inadequate control of symptoms by medica therapy.

Percutaneous transluminal coronary angioplasty (PTCA) has emerged as a new and exciting therapeutic option for patients with coronary artery disease. Since Grüntzig's initial report,[1] many investigators have confirmed the technical feasibility of angioplasty.[2–7] Furthermore, objective evidence of improved coronary flow[4,5] and improved cardiac function has been pre sented.[6,7] The long-term effects of PTCA on patier survival, morbidity, and functional capacity are ur known. Hence, the relative merits of PTCA, coronar bypass surgery, and medical therapy remain uncertai To provide an appropriate standard of comparison fo patients undergoing PTCA, we determined the outcom of all patients seen at Duke University Medical Cente before PTCA became available who would have bee suitable for PTCA had they presented today.

Methods

The computerized medical information system at Duk University Medical Center used in this study contains sta dardized clinical and laboratory information collected pr spectively on all patients undergoing cardiac catheterization These patients have been followed up at regular intervals t determine survival, subsequent myocardial infarction, an functional status.

Screening criteria for the study conformed closely to th current standards for PTCA.[1,2] All patients with the followir

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TABLE I Reasons for Exclusion of Patients Upon Review of the Coronary Angiogram

Characteristic	Patients (n)
Inaccessible narrowing*	57
Tandem narrowing	37
Eccentric lumen	28
Ventricular function	21
Bifurcation narrowing	20
Length of narrowing	19
Distal narrowing	17
Additional branch narrowing	11
Calcific deposits	4

* Too much curvature, 35; vessel tortuous, 10; lesion too eccentric to cross, 6; miscellaneous, 6.

TABLE II Comparison of Baseline Characteristics

Characteristic	Duke PTCA Candidates	NHLBI PTCA Registry[3]	Duke 2- and 3-Vessel CAD
Patients (n)	110	631	2,398
Age (mean ± SD)	49.5 ± 8.6	51	59.5 ± 8.4
Sex (% men)	55	78	86
Diabetes mellitus (%)	6	9	13
Systemic hypertension (%)	25	?	40
Cigarette smoker (%)	66	72	73
Family history of CAD (%)	49	?	54
Total cholesterol >250 mg/dl (%)	34	25	36

CAD = coronary artery disease; NHLBI = National Heart, Lung, and Blood Institute; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

TABLE III Comparison of Clinical Characteristics

Characteristic	Duke PTCA Candidates	NHLBI PTCA Registry[3]	Duke 2- and 3-Vessel CAD
Patients (n)	110	631	2,398
Duration (mo) of CAD (median)	7	6	28
NYHA class III or IV (%)	92	60	78
Preinfarction angina (%)	7	?	7
Progressive angina (%)	44	?	46
Peripheral vascular disease (%)	3	?	7
Cerebrovascular disease (%)	0	?	2

Mo = months; NYHA = New York Heart Association; other abbreviations as in Table II.

TABLE IV Comparison of Catheterization Characteristics

Characteristic	Duke PTCA Candidates	NHLBI PTCA Registry[3]	Duke 2- and 3-Vessel CAD
Patients (n)	110	631	2,398
Vessels (mean ± SD)	1 ± 0	1.16 ± 0.48	2.62 ± 0.48
LAD narrowed (%)	75	63	89
LC narrowed (%)	8	6	79
Right narrowed (%)	17	24	81
EF <50% (%)	19	5	47
EF <40% (%)	2	?	21

EF = left ventricular ejection fraction; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; other abbreviations as in Table II.

characteristics were identified: chest pain of New York Heart Association (NYHA) class II or greater, significant (≥75% narrowing of luminal diameter) subtotal stenosis in the proximal third of a single major coronary artery, and <75% distal coronary disease in that vessel. Only patients catheterized from 1969 through December 1980 were screened, because PTCA was begun in early 1981 at Duke University Medical Center.

Coronary angiograms from these patients were reviewed by a single angiographer (YK) experienced in performing PTCA. A coronary lesion was judged suitable for PTCA if it had the following characteristics: single, proximal, no more than slightly eccentric, not calcified, no longer than 1.5 cm, not located at or extending into branch vessels, and accessible to a dilating catheter. In addition, the vessel distal to the lesion had to be free of significant disease, and ventricular function had to be well preserved. Each characteristic was recorded separately, and an overall judgment of the suitability of both the lesion and the patient for PTCA was made.

Documentation of the functional capacity of angioplasty candidates was of particular interest in this study. The standard New York Heart Association (NYHA) classification system has been used routinely in the Duke medical computerized information system. However, a more reliable assessment of functional capacity may be possible using the recently developed Specific Activity Scale (SAS), which classifies patients by their ability to perform a set of common daily activities.[9] SAS class I indicates the least functional impairment, whereas SAS class IV indicates the most. All patients were mailed a detailed functional assessment questionnaire to supplement the routine follow-up information and to define more precisely their current functional status with the SAS. However, retrospective reclassification of previous NYHA functional assessments was not feasible. The questionnaire also determined the frequency and severity of chest pain, subsequent hospitalizations, and employment history.

Cumulative survival rates from the time of catheterization were calculated by standard life-table methods.[10] Patients treated initially with medical therapy and subsequently with coronary bypass surgery were included in the medical group until surgery. Surgical survival curves were calculated beginning the day of operation. Patients receiving bypass surgery at other hospitals were excluded from the surgical survival curves. Breslow's formulation[11] of the Cox proportional hazards model[12] was used to analyze the relation between baseline characteristics and survival.

Results

Of the 5,126 patients catheterized at Duke University for suspected coronary disease during the study period, 223 (4.4%) met the initial screening criteria. Fifteen patients were excluded from further analysis: cineangiograms could not be located for 13 patients and had deteriorated too greatly to review in 2 other patients.

Of the 208 patients whose coronary angiograms were reviewed, 110 (53%) were judged suitable candidates for angioplasty. Thus, 2.1% of the total population catheterized at Duke University Medical Center during this time period were angioplasty candidates. The reasons for excluding patients whose angiograms were reviewed are summarized in Table I. Most patients were excluded for more than 1 unacceptable angiographic finding: 27

for a single reason, 35 for 2 reasons, 27 for 3 reasons, and 9 for 4 reasons.

The baseline characteristics of patients suitable for PTCA are summarized in Tables II through IV. For comparison, these tables also present the baseline characteristics of 2 other groups: (A) the first 631 patients enrolled in the National Heart, Lung, and Blood Institute's (NHLBI) PTCA registry,[3] and (B) patients with 2- and 3-vessel coronary artery disease catheterized at Duke during the study period. The Duke PTCA candidates are quite similar to patients enrolled in the NHLBI PTCA registry.

The proportion of patients suitable for PTCA, treated medically, who were alive during follow-up is displayed in Figure 1, and the proportion without cardiovascular events during follow-up is displayed in Figure 2. Five years after catheterization 97% were alive, and 85% were alive and free of interval myocardial infarction. All deaths occurred in patients with disease of the left anterior descending coronary artery, but differences in survival according to the vessel involved were not statistically significant.

Of the 110 angioplasty candidates, 56 (51%) subsequently underwent coronary artery bypass grafting; 46 patients underwent early surgery (within 6 months of catheterization); the remaining 10 patients underwent surgery at a later time. Operative therapy in patients with single-vessel coronary disease is generally limited at Duke to those whose symptoms are not controlled sufficiently by adequate medical therapy. This policy is reflected by a significantly higher dose of propranolol received by the patients who underwent bypass surgery as compared with those who did not.

The survival curve of angioplasty candidates who underwent coronary artery surgery is displayed in Figure 3. Five years after surgery, 91% of the patients were alive and 87% were free of myocardial infarction. Two patients died within 30 days of operation; 1 died of a ruptured abdominal aortic aneurysm 9 days postoperatively, and another died of an apparent intraoperative myocardial infarction. Four patients had coronary artery surgery performed after repeat cardiac catheterization demonstrated progressive coronary disease. These 4 patients were excluded from calculations of postoperative survival, because they were no longe angioplasty candidates at the time of their operation However, 3 other patients in whom the preoperativ repeat cardiac catheterization demonstrated no chang in the suitability of the lesion for PTCA were include in the surgical survival curve. Two patients who un derwent coronary bypass surgery at other hospitals wer also excluded from the surgical survival analysis. All excluded patients were alive as of May 1982.

Patients suitable for angioplasty had a prognosis tha was indistinguishable from that of other medicall treated patients with single-vessel disease from Duke when tested univariately with the Cox proportiona hazards model.[12] Only ejection fraction was significantl related to survival among angioplasty candidates identical to the finding in the entire group of patient with single-vessel disease.[13]

Of the 46 PTCA candidates who underwent earl coronary bypass surgery, 77% were improved by 1 o more NYHA classes at the initial 6-month follow-u contact, and 67% were class I or II. However, 78% o PTCA candidates who remained on medical therap had improved by 1 or more NYHA classes at the 6 month follow-up contact, and 66% were NYHA class or II. A preliminary report from the NHLBI registry[1] indicated that 77% of patients improve after PTCA b

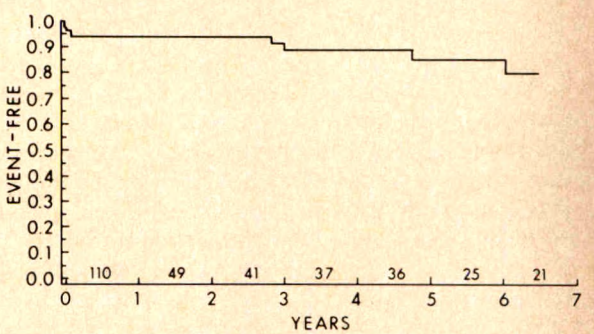

FIGURE 2. Cumulative probability of remaining free of a cardiovascula event (death or myocardial infarction) in patients suitable for percuta neous transluminal coronary angioplasty and treated with medica therapy. The numbers above the horizontal axis denote the number o patients under observation during the interval.

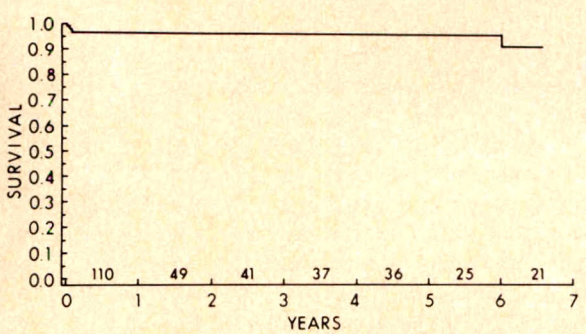

FIGURE 1. Cumulative probability of survival in patients suitable for percutaneous transluminal coronary angioplasty and treated with medical therapy. The numbers above the horizontal axis denote the number of patients under observation during the interval.

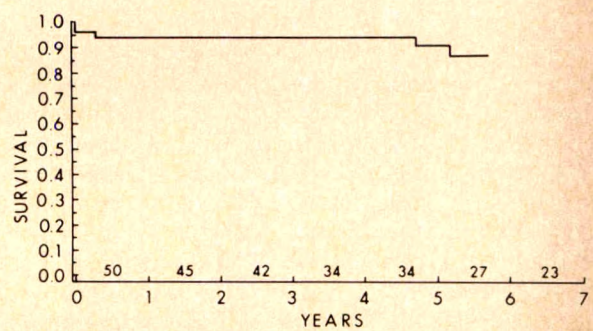

FIGURE 3. Cumulative probability of survival in patients suitable fo percutaneous transluminal coronary angioplasty and treated with co onary artery bypass surgery. The numbers above the horizontal axi denote the number of patients under observation during the interval

1 or more functional classes of the closely related Canadian Cardiovascular Society grading system.

We attempted to contact all patients and obtain detailed information about their employment history and current functional capacity. Responses were obtained from 91 of the 94 patients who were alive. Forty-eight of the 56 patients (86%) working before cardiac catheterization were still working full or part time 6 months after catheterization. Twenty-three patients ceased working before catheterization and never resumed, and 12 patients never worked outside the home.

Information about functional ability as of May 1982 was also obtained by questionnaire. The median follow-up period was 6.5 years, with a range of 1.4 to 12.2. Fourteen patients (15%) were hospitalized because of heart disease in the past year; none had a documented myocardial infarction. Thirty-four patients were still employed; 19 have been treated medically and 15 have been treated surgically. Functional capacity was assessed by the SAS: 36 patients (40%) were SAS functional class I (21 medically treated and 15 surgically treated), 30 (33%) were SAS class II (12 medically treated and 18 surgically treated), 23 (25%) were SAS class III (10 medically treated and 13 surgically treated), and 1 surgically treated patient was functional class IV. One patient refused to answer questions related to functional capacity.

Of the 110 Duke angioplasty candidates, 42 (38%) had coronary angiography repeated on a subsequent occasion. The repeat procedure was performed for a clinical indication in 34 patients and according to a study protocol after coronary bypass surgery in 8 patients. A decrease in the luminal diameter or the appearance of new lesions at subsequent coronary angiography was considered progressive coronary disease. Five of the 8 patients (62%) with repeat catheterization performed within 12 months displayed disease progression in the vessel originally involved; none had progression involving additional vessels. Ten of the 15 patients (67%) with repeat catheterization performed between 13 and 24 months displayed disease progression; 5 of these patients (33%) had progression involving additional coronary vessels. Twelve of the 18 patients (67%) with repeat catheterization performed more than 24 months after the original procedure displayed disease progression; 7 (39%) of these patients had progression involving additional coronary vessels.

Discussion

In this study we wished to characterize the natural history of patients suitable for PTCA in order to provide a standard of comparison for patients undergoing PTCA. In the absence of a randomized controlled trial, this method provides the best alternative available to judge the long-term efficacy of PTCA. We first identified all potential candidates for PTCA among patients who underwent cardiac catheterization at Duke University between 1969 and 1980. The coronary angiograms of these potential candidates for angioplasty were then carefully reviewed and their actual suitability for the procedure was established. The clinical characteristics of these patients closely resemble those of the patients in the NHLBI's registry of patients undergoing PTCA.

Our major finding was the excellent prognosis of patients suitable for PTCA. Ninety-seven percent of medically treated PTCA candidates survived 5 years. Furthermore, 85% of medically treated patients suitable for PTCA were alive and had not had myocardial infarction after 5 years of follow-up. This excellent prognosis probably results from the good left ventricular function and limited coronary atherosclerosis in PTCA candidates.[13,15] Forty-six patients (42%) underwent coronary artery bypass surgery within 6 months of cardiac catheterization, and 10 other patients underwent late operation. The 5-year survival and event-free rates in the surgically treated patients were also very good, 91 and 87%, respectively. Unfortunately, the number of patients studied does not permit any statistically meaningful comparisons between the prognosis of those treated medically and that of those treated surgically. Studies in larger groups have failed to demonstrate a difference in prognosis between medically and surgically treated patients with single-vessel disease.[13,16–18] These findings suggest that the prognosis of angioplasty candidates is indistinguishable whether angioplasty, coronary bypass surgery, or medication is chosen as therapy.

In view of the excellent prognosis of PTCA candidates, the efficacy of the procedure in improving functional capacity becomes an important consideration. Although data regarding functional status lack the precision of events such as death or myocardial infarction, they can provide a valuable perspective. The functional outcome of PTCA candidates was very good with medical therapy and subsequent coronary artery bypass surgery if needed. Seventy-eight percent of all PTCA candidates had improved by 1 or more functional classes by the 6-month follow-up contact, and 66% were NYHA class I or II. Eighty-six percent of all patients working at the time of catheterization were still employed 6 months later. Both functional capacity and employment were well maintained in most patients who initially responded to medical therapy, with only 20% later undergoing coronary bypass surgery during long-term follow-up. These findings demonstrate that good functional results can be obtained with medical therapy in many patients suitable for angioplasty.

Although many angioplasty candidates will improve with vigorous medical management, some will be refractory to therapy. The likelihood of coronary disease progression in patients with refractory symptoms may determine whether they should receive angioplasty or coronary bypass surgery. Over one-third of the PTCA candidates in this study underwent repeat cardiac catheterization on a subsequent occasion. Although no patient had documented disease progression in additional vessels in the first year, 36% of patients in subsequent years did. This figure probably represents an upper limit to the true percentage, as most of these patients were recatheterized for clinical indications such as increasing or recurring symptoms. Nonetheless, these data suggest that many PTCA candidates will ultimately require a second revascularization procedure.

As repeat coronary bypass surgery is technically more difficult and carries greater risk, angioplasty may be a better initial approach in suitable patients with refractory symptoms.

The patients described here represent a historical control group for PTCA. Such control groups are subject to several well recognized limitations. Changing diagnostic standards over time may confound comparisons when historical controls are used. Because we selected patients for this study according to current standards for PTCA, this problem has been avoided. However, indications for PTCA will broaden as experience with the procedure grows and the technique is further improved. Note that only patients with coronary lesions of ≥75% luminal narrowing were included in this series; including patients with 50% coronary lesions would have improved the observed outcomes.[19] Evolution of therapeutic methods also limits the utility of historical comparison groups. New drugs have been introduced (such as calcium channel blocking agents), surgical methods have been refined (such as cardioplegia), and total cardiovascular mortality has declined over the past 12 years; these and other developments may also confound our findings. However, therapy has probably improved over this period, and PTCA candidates probably would receive better care and experience better outcomes today than are reported here.

This study used an observational data bank that included patients seen at 1 institution over a 12-year period. The advantages and limitations of this approach are widely recognized.[20] The clinical management of these patients was the responsibility of several cardiologists, and no strict protocol was followed. Consequently, the independent effect of any 1 component of therapy on functional capacity cannot be completely separated from another. For instance, the clinical outcome of patients maintained on medical therapy may have been influenced by the availability of coronary bypass surgery for those whose symptoms cannot be controlled adequately. Conversely, the clinical outcome of patients who underwent coronary artery bypass grafting may have been affected by the availability of medical therapy before and after the operation. Our findings do support the value of the conservative therapeutic approach generally followed at Duke University Medical Center that consists of adequate medical therapy and subsequent revascularization if needed in patients with single-vessel coronary artery disease.

Introduction of a new therapeutic method usually prompts calls for a randomized, controlled trial to judge its efficacy. Our findings imply that very large sample sizes are necessary for a randomized trial of PTCA, as undesirable outcomes occur so infrequently in suitable patients. For instance, a trial randomizing a total of 7,600 patients would have only an 80% chance of documenting an actual 33% reduction in mortality over 5 years (that is, alpha = 0.05, beta = 0.80). A total of 1,400 patients would have to be randomized to document a 33% reduction in cardiac events at the same level of reliability. More patients are required to detect smaller reductions in event rates or to attain higher reliability. Such a trial would be very expensive and would take years to complete. Meanwhile, the techniques of PTCA, coronary bypass surgery, and medical therapy woul continue to evolve, reducing the relevance of the trial findings. Thus, a randomized trial of PTCA with deat or myocardial infarction or both as a primary end poir seems highly impractical. However, a trial with en points such as left ventricular function, exercise ca pacity, or medical costs should require fewer patient and less time; such a trial may be feasible.

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Detrimental Effect of Propranolol in Patients With Coronary Arterial Spasm Countered by Combination With Diltiazem

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This study determines, with quantitative variables, if propranolol is detrimental in patients with documented coronary arterial spasm and if this drug can be used in combination with calcium antagonists. Eleven patients with documented coronary spasm were entered prospectively in a study with 4 phases of 2 days each: (1) control, (2) diltiazem or propranolol (mean 225 ± 75 mg/day), (3) propranolol or diltiazem (360 mg/day), (4) propranolol and diltiazem. The effects of the drugs were assessed by the detection of ischemic electrocardiographic episodes (24-hour electrocardiographic monitoring) and provocative tests with ergonovine. During the period of treatment with propranolol, the number and the duration of attacks increased and provocative tests had positive results in all patients. Diltiazem completely abolished spontaneous episodes, but 6 of 11 patients remained sensitive to the administration of ergonovine. The association of the 2 drugs led to a disappearance of ischemic episodes. In conclusion, propranolol is ineffective in patients with coronary artery spasm. It can be used in combination with diltiazem, but without any advantage over diltiazem alone.

The efficacy of beta-adrenoreceptor blockers in effort angina is well established. However, the effect of beta blockade on coronary artery spasm is controversial. In 1971 and 1975, Guazzi et al[1,2] reported a reduction in the number of attacks of variant angina in patients who received a large dose of beta-blocking drugs. Other investigators[3–6] have reported that propranolol was detrimental in the treatment of coronary artery spasm. The purpose of this study was to establish the effects of propranolol in patients with documented coronary artery spasm, to compare this drug with diltiazem, a calcium antagonist, and to evaluate the effects of the 2 drugs combined.

Methods

We studied 11 patients (10 men and 1 woman) aged 43 to 69 years (mean age 50). They had angina at rest with ≥1 mm of S-T segment elevation during the attacks. Five patients also had angina on effort. Coronary arteriography showed significant (>75%) vessel disease in 6 patients; however, only small irregularities or normal vessels were noted in 5 patients. All of these patients had a coronary arterial spasm documented by coronary arteriography and defined as a transient, reversible subtotal or total narrowing of a major epicardial coronary branch associated with objective evidence for myocardial ischemia. Spasm was located on the right coronary artery in 6 patients, on the left anterior descending coronary artery in 2, and on the circumflex branch in 3.

The patients were studied over 9 days. The study consisted of 4 phases (Fig. 1). Phase 1 consisted of 2 days without treatment (control period). At the end of this phase, the patients were randomized to therapy with propranolol or diltiazem during the 2 days (Phase 2). They were then crossed over to the opposite drug regimen (Phase 3). Between Phases 2 and

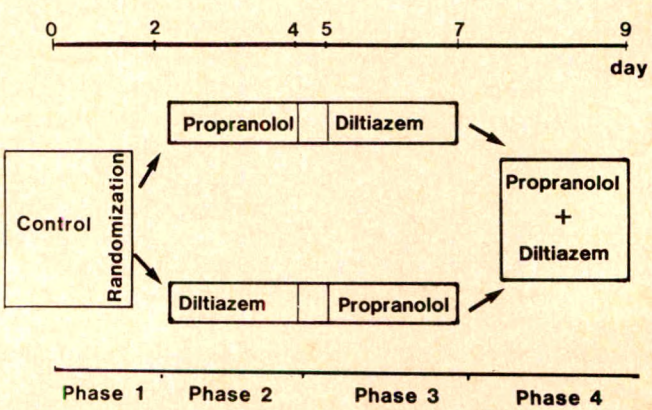

FIGURE 1. The design of the protocol.

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TABLE I Clinical Data and Results of 24-hour Holter Monitoring

Patient	Age (yr) & Sex	Vessel Disease	Location of Coronary Spasm	Number of Ischemic Episodes in Phases			
				1	2	3	4
1	45M	1	Right	3	6	0	0
2	45F	NS	LAD	2	6	0	0
3	49M	1	LC	4	5	0	0
4	52M	NS	Right	5	4	0	0
5	48M	NS	LC	4	4	0	0
6	48M	1	LC	5	5	0	0
7	69M	2	Right	7	10	0	0
8	43M	3	Right	4	4	0	0
9	41M	NS	LAD	3	7	0	0
10	50M	NS	Right	6	6	0	0
11	60M	1	Right	3	6	0	0

LAD = left anterior descending coronary artery; LC = left circumflex branch; NS = nonsignificant stenosis; Right = right coronary artery.

3, there was 1 day without treatment to wash out the effects of the drug. During Phase 4, the patients received the 2 drugs over 2 days. The dosage of propranolol (225 ± 75 mg/24 hours, mean ± standard deviation) was adjusted to obtain a heart rate of 50 to 60 beats/min. Diltiazem was given in a standard dosage of 360 mg/24 hours. During Phase 4, the patients received a high dose of diltiazem (60 mg 6 times a day) and propranolol at the same dose as in Phase 1. During each phase, a 24-hour ambulatory monitoring was recorded on day 1 and 2. The monitoring was performed in 2 leads (CM5—manubrium; V_5 and C′M5—manubrium V_{5R}). Ischemic episodes were detected by S-T segment changes (decrease or increase) >1.5 mm. The results were assessed by the number, the duration of ischemic episodes, and the presence or absence of arrhythmias. Mean heart rate during the day was also calculated. On the second day of each phase, a provocative test with ergonovine was performed at 11:30 A.M. The tests started with an intravenous injection of 0.1 mg of methylergonovine. In the absence of electrocardiogram changes, a second dose of 0.2 mg was injected 5 minutes later; if there was no response, a third (0.3 mg) and a fourth dose (0.4 mg) were administered at intervals of 5 minutes. The electrocardiogram (12-lead) was carefully monitored and the criterion for a positive test was an S-T segment change >1 mm. The test was considered to be negative if 10 minutes after the last injection (1 mg = 0.1 + 0.2 + 0.3 + 0.4) the electrocardiogram was unchanged. If the test showed S-T segment changes >1 mm, intravenous isosorbide dinitrate (3 mg) was immediately injected. This procedure resulted in no complications.

The results of ergonovine testing were compared with 2 statistical tests. Since the variable was neither continuous nor normally distributed, a nonparametric test was required, and the chi-square test was used; but in the patients whose tests had positive results during treatment, a comparison of dose levels was performed with a paired *t* test.

Results

Effects on heart rate: Mean heart rate during the day was significantly lower in Phases 2, 3, and 4 than during the control period (Phase 1). When the patients received propranolol, the mean heart rate was 53.6 ± 8.6 beats/min. Diltiazem also decreased heart rate (from 77.3 ± 12.4 to 64.1 ± 8.2 beats/min, $p < 0.01$). When propranolol and diltiazem were used, heart rate decreased 48.8 ± 3.1 beats/min. This tendency to bradycardia could be a limitation to the use of this drug combination.

Comparison of Phase 1 (control period) an phase of propranolol treatment: During the contr period, 46 attacks were detected by Holter monitorin (Table I) over a period of 150 minutes for the whol group. Seven attacks were complicated by arrhythmia (run of premature ventricular beats). Some patients ha more attacks with propranolol treatment than durin the control period, but others had fewer ischemic ep sodes with propranolol. For the group, the number attacks increased from 46 to 63 and the total duratio reached 235 minutes during the phase with propranolo Six attacks were complicated by runs of prematu ventricular beats; one patient had a short run of ver tricular tachycardia. Provocative tests always ha positive results during the control period and the mea dose of ergonovine inducing S-T segment changes > mm was 0.47 ± 0.09 mg. The amplitude of S-T segmer changes was 2.18 ± 0.81 mm (mean ± standard error the mean). During the period of treatment with pr pranolol, the tests had positive results in all patient (Table II). The dose of ergonovine (0.49 ± 0.17 mg) wa not significantly different from the dose during th control period. The maximum amplitude of S-T seg ment changes (3.4 ± 0.72 mm) was higher ($p < 0.0$ during treatment with propranolol than during th control period. Thus, the 24-hour ambulatory mon toring clearly showed a detrimental effect of propra olol. However, the provocative test, which had positiv results in all patients, demonstrated a similar reactivit of the patients with propranolol and during the contr period.

Comparison of Phase 1 (control period) an phase of diltiazem treatment: Provocative test result were significantly different (chi-square = 6.97, $p < 0.0$ during the 2 periods; when the patients were treate with diltiazem, the ischemic episodes totally disap peared and Holter monitoring did not reveal S-T seg ment changes or arrhythmias (Table I). The test ha negative findings in 5 patients but had positive result in 6 patients (Table II). In this latter group, the dose ergonovine inducing positive test results (0.48 ± 0.1 mg) was slightly but insignificantly higher than durin the control period (0.37 ± 0.08 mg). Thus, from thes results, we conclude that diltiazem was very effectiv and completely abolished spontaneous ischemic epi

TABLE II Results of Ergonovine Provocative Tests

	Phase 1		Phase 2		Phase 3		Phase 4	
Patient	Dose	S-T↑	Dose	S-T↑	Dose	S-T↑	Dose	S-T↑
1	+0.3	1.5	+0.1	2	−1	. . .	+1	1.5
2	+0.6	3	+0.3	10	+0.6	2	+1	4
3	+0.1	2	+0.3	3	+0.1	1.5	+0.6	3
4	+0.6	2.5	+0.6	3	−1	. . .	−1	. . .
5	+0.3	3	+0.3	3	+0.3	2	+0.6	2
6	+0.6	1	+0.6	1	+0.6	1	+0.6	1
7	+0.3	3	+0.1	3	+0.3	2	+0.3	2
8	+1	1	+1	1	−1	. . .	−1	. . .
9	+0.1	1.5	+1	4	−1	. . .	−1	. . .
10	+0.3	2.5	+0.1	3	+1	2	+0.6	2
11	+1	3	+1	4	−1	. . .	+1	2
Mean ± SEM	0.47 ± 0.09	2.18 ± 0.81	0.49 ± 0.17	3.4 ± 0.7	. . .	. . .	. . .	. . .

Dose = dose of ergonovine; SEM = standard error of the mean; S-T↑ = S-T segment elevation (mm); + = positive test result; − = negative test result.

sodes; but at a dose of 360 mg/day, 6 of 11 patients remained sensitive to the administration of ergonovine. No adverse effects were observed during the short period of treatment with diltiazem.

Results of treatment with diltiazem and propranolol combined: The combination of diltiazem and propranolol led to a disappearance of ischemic episodes on 24-hour electrocardiographic monitoring. No S-T segment changes or arrhythmias were observed (Table I). During the provocative tests, only 3 patients had a negative test result and 8 had a positive test. However, the dose of ergonovine inducing S-T segment changes >1 mm (0.71 ± 0.1 mg) was higher during treatment with propranolol and diltiazem than during the control period (0.44 ± 0.1 mg) ($p < 0.05$) (Table II). If we compare propranolol alone with propranolol and diltiazem, the combination is better. The ischemic episodes disappeared but the chi-square test did not show a significant difference in the provocative test results. However, the question arises as to the advantages of diltiazem and propranolol over diltiazem alone. The Holter monitoring findings revealed no difference. However, the provocative test findings revealed that the 6 patients whose test results were positive during treatment with diltiazem had positive findings when this drug was used with propranolol. (Two had positive results with the same dose of ergonovine, 3 with a higher dose, and 1 with a lower dose.) However, 2 tests that had negative results during treatment with diltiazem alone had positive findings with propranolol and diltiazem. In fact, for the whole group, there was no significant difference for the dose of ergonovine inducing S-T segment changes in each phase (diltiazem alone versus propranolol and diltiazem). Finally, we can conclude that the combination of propranol and diltiazem has no apparent advantage over diltiazem alone. No adverse effects were observed with the combination of propranolol and diltiazem, but heart rate decreased to 48.8 ± 3.1 beats/min.

Discussion

The evaluation of a treatment in patients with coronary arterial spasm is very difficult. The results must be interpreted with caution because of the wide spontaneous variability of symptoms. Patients with vasospastic angina can have frequent attacks during the active phase of the disease, while the attacks disappear during a quiescent period. Thus, the effects of a drug must be assessed over a short period. Moreover, the trials had to take account of the frequency of asymptomatic ischemic episodes.[7] Sixty-four percent of ischemic episodes demonstrated by 24-hour electrocardiographic monitoring are asymptomatic[8]; in general, S-T segment changes are symptomatic if they persist for >3 minutes but are asymptomatic if they are shorter.[6] Thus, the evaluation of the effects of drugs in coronary arterial spasm requires a trial of short duration in order to study the patients in active phase and with objective tests. Holter monitoring can detect spontaneous ischemic episodes (even though asymptomatic) and provocative tests (with incremental doses of ergonovine) can assess the reactivity of the patients. Some workers[9] have questioned the reproducibility of the test; others[10] consider the provocative test reproducible and a good means of assessing the efficacy of a drug. In our study, the protocol lasted 9 days and the assessment was made with objective tests.

Propranolol leads to reduction in heart rate, blood pressure, and myocardial contractility, decreasing myocardial oxygen demand. In patients with angina related to coronary artery spasm, Maseri et al[11] demonstrated that myocardial oxygen demand was unchanged before the attack and that ischemia results from a decrease in myocardial oxygen supply. Thus, it is illogical to treat such patients with beta-blocking agents. However, the direct effect of beta blockers on vascular receptors can play an important role because beta-adrenergic blockade can unmask alpha-adrenergic vasoconstriction. Some investigators[12,13] have suggested that an increase of sympathetic activity with a stimulation of alpha adrenoreceptors can induce coronary artery spasm. Ricci et al[14] reached the same conclusions in relieving spasm with phentolamine or preventing the recurrence of attacks with phenoxybenzamine. However, Robertson et al[15] found no modification of various indexes of sympathetic nervous system function in patients with Prinzmetal's variant angina. Thus, theoretically, the beta-blocking agents can indirectly induce

a more intense vasoconstriction and are contraindicated in patients with coronary artery spasm. Clinically, there are controversial results with propranolol in patients with Prinzmetal's variant angina. Guazzi et al[16] reported satisfactory results in patients with variant angina; beta blockers fully abolished the symptoms in 73% of the cases as evaluated in subjective (pains reported) and objective terms (ECG alterations documented during continuous recordings). However, the doses of propranolol were very high (mean 390 mg/day, range 160 to 800).

In contrast, several reports[17,18] detail poor results with propranolol. More recently, Robertson et al,[6] using a double-blind protocol with quantification of ischemia by electrocardiographic recording, showed that at low doses (40 mg every 6 hours) or high doses (160 mg every 6 hours), the duration of attacks was significantly prolonged, but the frequency was not. In our study assessing propranolol with quantitative variables, the number and the duration of the attacks were significantly higher during the treatment with propranolol than during the control period. In contrast, the response of the patients to ergonovine was not significantly different. Consequently, we agree with the conclusions of Robertson et al[6] that propranolol as the only therapy is frequently detrimental in angina due to coronary artery spasm and should not be used alone in the treatment of this disorder.

In contrast, calcium antagonists are very effective.[19,20] In our study, we observed that diltiazem completely abolished the ischemic episodes. However, in contrast to the disappearance of ischemic episodes, ergonovine tests had positive results in some patients. Obviously, it can be argued that ergonovine is an artificial means of provoking spasm and that the disappearance of attacks on electrocardiographic monitoring means that the drug is really very effective; however, in some patients the reactivity of the vessel to ergonovine persists despite treatment.

The combination of propranolol and calcium antagonists can logically be used in patients with spasm superimposed on organic fixed narrowing who have angina at rest and on effort. In our study, the combination of propranolol and diltiazem had the same effect as diltiazem alone on the spontaneous ischemic episodes. However, we did not perform exercise tests during the control period and the phase with both drugs combined. This investigation should be of interest in evaluating the effects of exercise capacity, especially in the patients with fixed organic narrowing. Although we did not observe spontaneous ischemic episodes with combined treatment by diltiazem and propranolol, in addition to the 6 patients with a positive ergonovine test resu during diltiazem therapy, 2 other patients became r active to ergonovine.

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Long-Term Prognosis After First Q-Wave (Transmural) or Non–Q-Wave (Nontransmural) Myocardial Infarction: Analysis of 593 Patients

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Follow-up results in 593 patients ≤7 years (mean 4.7) after hospital discharge for their first myocardial infarction (MI) are presented. Patients were grouped according to the presence or absence of Q waves on electrocardiograms after the MI and by peak serum glutamic oxalacetic transaminase (SGOT) level during hospitalization. Cardiac mortality varied. Patients with Q-wave infarcts and an SGOT level ≤240 IU/liter had a cardiac mortality of 3.1% per year, whereas patients with Q-wave MI and an SGOT level >240 IU/liter had an 11% 6-month mortality and a 3.8% per year cardiac mortality thereafter. However, patients with non–Q-wave (nontransmural) MI had a excellent survival rate for 2 years (96.8%) which continued in patients aged ≤60 years thereafter. However, patients with non–Q-wave infarcts aged >60 years had a 12% per year cardiac mortality in the third post-MI year and an additional 12% died each year thereafter. Early mortality was related to enzyme level, whereas late mortality was a function of type (Q-wave or non–Q-wave) and age.

The prognosis of patients discharged from the hospital after a first non–Q-wave (nontransmural) or Q-wave (transmural) myocardial infarction (MI) has been the subject of numerous studies,[1–6] but the findings have been largely inconclusive and conflicting. However, in many studies, either the number of patients with nontransmural MI was small (<25)[1,4] or a substantial percentage of patients with previous MI[2,3,6] were included. Mahony et al[1] recently showed that the prognosis of patients with nontransmural MI and no previous MI was much better than that of patients with nontransmural MI who had had a previous MI. Thus, separating patients with a first MI from those with multiple MIs seems one way of deriving meaningful findings.

We previously showed that patients with first non–Q-wave (nontransmural) MI usually had a relatively small MI and a lower in-hospital mortality rate than patients with Q-wave (transmural) MI.[7] The present study establishes the prognosis of patients after hospital discharge for their first Q-wave or non–Q-wave MI. Features of the original MI which are useful in predicting survival over this period are identified.

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Methods

Criteria for selection: Subjects were selected from consecutive patients aged ≤75 years admitted <48 hours after MI to the coronary care unit at either the Jewish Hospital of St. Louis or Barnes Hospital between November 1971 and June 1975. The age limit was selected to focus on persons who might be candidates for aggressive management of their coronary disease. Patients were excluded if there was any evidence of previous MI or if they had persistent left bundle branch block. All patients' electrocardiograms were continuously monitored for the first 3 days of hospitalization and standard 12-lead electrocardiograms and serum enzyme levels (creatinine kinase [CK], serum glutamic oxalacetic transaminase, aspartate transaminase, [SGOT], lactate dehyrogenase [LDH], and heat stable LDH or alpha hydroxy butyl dehydrogenase) were obtained daily for 3 days according to a prescribed protocol.

The diagnosis of MI was made if these 2 criteria were met: (1) a clinical history compatible with MI, and (2) serum enzyme changes typifying MI with at least 1 value exceeding 1.5 times the upper limits of normal. The electrocardiographic diagnosis of Q-wave MI required pathologic Q waves (0.04 second in duration and amplitude >25% of the R wave) or, for

TABLE I Data on the Infarction Groups

A. Selected Characteristics of the Infarction Groups

Variable	Q-Wave n	Q-Wave %	Non–Q-Wave n	Non–Q-Wave %	p Value
Male	363	73	64	68	0.3812*
Cigarette smoker	225	45	52	55	0.0722
Previous hypertension	182	37	44	48	0.0617
Diabetes	86	17	14	15	0.6536
Caucasian	423	85	72	77	0.0679
Cardiomegaly	196	39	36	38	0.9086

B. Age and Enzyme Levels of the Infarction Groups

Variable	Q-Wave Mean	Q-Wave 95% CI†	Non–Q-Wave Mean	Non–Q-Wave 95% CI	p Value
Age (yr)	58.2	57.7–58.7†	56.6	55.4–57.8	NS
Peak SGOT	173.8	164.1–184.1	107.5	95.9–120.6	0.0001
Peak LDH	617.7	590.0–646.6	401.9	368.2–438.6	0.0001
Total patients	499		94		

* Fisher's exact test (2-tail).
† 95% confidence intervals for mean.
LDH = lactate dehydrogenase; NS = not significant; SGOT = serum glutamic oxalacetic transaminase (aspartate transaminase).

posterior MI, pathologic R waves (0.04 second in duration with RV_1/SV_1 or $RV_2/SV_2 > 1$), these changes associated with evolving ST-segment and T-wave changes in appropriate leads.[8] The diagnosis of non–Q-wave MI was made when the electrocardiogram did not meet QRS criteria for Q-wave MI but history and enzymes confirmed the presence of acute infarction.

Data management: Demographic and clinical information was obtained prospectively[7] from the patients' charts as well as from direct patient interviews by trained personnel following a protocol. Records were analyzed using the Statistical Analysis Systems computer program.[9] The data were subjected to rigorous checks of consistency, and when questions arose, the patients' charts were reviewed. All electrocardiograms were reviewed by 2 of us (RJK, ST) independently to confirm the classification of MI.

Follow-up information was obtained by telephone or mail, first from the patient's physician and then, if necessary, from the patient. If a patient had died, the circumstances of the death were ascertained from family members or neighbors.[10] Death was classified by a panel of 4 cardiologists as: sudden death, sudden death/new MI, not sudden death/new MI, not sudden death/cardiac death, and noncardiac death. A new MI had to meet the same criteria as the index MI, from a review of hospital records or proof at postmortem examination. Deaths within 1 hour of the onset of symptoms and unexpected, unobserved deaths were classified as sudden.

Statistical methods: Demographic and clinical characteristics of patients with Q-wave and non–Q-wave MI were compared with Fisher's exact test (Table I). The log transforms of peak SGOT and peak LDH levels and mean ages for the 2 groups were compared using a 2-sample *t* test (Table I). Cardiac survival rates were plotted for the follow-up period by the method of Kaplan-Meier, with noncardiac deaths treated as censored data.[11,12]

The overall survival rate of patients with the 2 types of MI over the follow-up period was evaluated using Breslow's test for equality of survivorship functions.[12,13] The probability of death of patients in different subgroups at different time periods for the first 3 years was examined by performing 4 separate although nonindependent log rank tests[14] over the convenient intervals of 0 to 6, 6 to 12, 12 to 24, and 24 to 36 months (Table II). This analysis was not continued becau of large numbers of censored patients after 3.5 years. Howev the survival curves are carried out to 6 years (Figs. 1 to 4).

The prognostic value of various demographic and clinic variables obtained at the time of MI was assessed for the fi follow-up year and again for the third year (Table III). T variables chosen for analysis from the many available we those previously associated with post-MI mortality[7,15–20] those that reflected our interest in the type and size of i farction. Cardiomegaly was assessed from the admissi (usually portable) chest roentgenogram.

Multivariate analysis was carried out in a stepwise fashi using the Cox regression model.[21,22] Briefly, an unadjust chi-square statistic (Q statistic) was computed to assess t relationship between each variable and cardiac survival. T variable with the largest Q statistic (best relation) was add to the model and chi-square Q statistics, adjusted for variabl in the model, were computed for all variables not in the mod The variable with the largest adjusted Q statistic was th introduced into the model and the procedure repeated un no remaining variable contributed independent informati significant at the $p < 0.05$ level (Table IV).

Results

Study population: Five hundred ninety-three p tients aged ≤75 years were discharged after their fir MI and met criteria for our study. There were 499 p tients with Q-wave MI (84.2%) and 94 patients wi non–Q-wave MI (15.8%). Three patients with Q-wa MI were lost to follow-up during the first 3 years, givi a 99.5% complete follow-up for the first 3 years. T mean follow-up was 4.7 years and 175 patients we followed up for 6 years. The 3-year mortality was 19.6 (116 patients) overall, 20% of the group with Q-wave M (100 patients), and 17% of the group with non–Q-wave (16 patients).

Patients in both groups were similar with respect age, sex, race, and coronary risk factors (Table I). P tients with Q-wave MI had significantly higher pea SGOT and LDH levels than did those with non–Q-wa

TABLE II Interval Mortality by Type of Infarction* and Peak SGOT Level

	First 6 Months		6 to 12 Months		12 to 24 Months		24 to 36 Months	
	n	%	n	%	n	%	n	%
Q-wave SGOT ≤ 240 IU/liter	335		322		309		295	
Mortality	13	3.9	13	4.0	13	4.2	17	5.8
Cardiac mortality	9	2.7	10	3.1	8	2.6	10	3.4
Sudden death	6	1.8	6	1.9	5	1.6	6	2.0
New infarction	7	2.1†	9	2.8	8	2.7	12	4.3
Non–Q-wave	94		92		91		89	
Mortality	2	2.1	1	1.1	2	2.2	11	12.3
Cardiac mortality	2	2.1	0	0	1	1.1	10	11.2
Sudden death	1	1.1	0	0	0	0	6	6.7
New infarction	7	7.4	1	1.1	4	4.7	2	2.5
Q-wave SGOT >240 IU/liter	164		144		140		132	
Mortality	20	12.2	4	2.9	8	5.7	12	9.1
Cardiac mortality	18	11.0	2	1.3	8	5.7	9	6.8
Sudden death	9	5.5	2	1.3	4	2.9	5	3.8
New infarction	10	6.1	3	2.2	2	1.5	5	4.1
Log rank test results	593		558		540		516	
Mortality	p = 0.0002		p = 0.3473		p = 0.4359		p = 0.0928	
Cardiac mortality	p = 0.0001		p = 0.1505		p = 0.1065		p = 0.0139	
Sudden death	p = 0.0277		p = 0.4145		p = 0.2536		p = 0.0778	
New infarction	p = 0.0180		p = 0.6370		p = 0.3808		p = 0.7759	

* Non–Q-wave = non–Q-wave infarction; Q-wave = Q-wave infarction; other abbreviations as in Table I.
† n for new infarctions = number of survivors at beginning of period who have not had a new infarction before the onset of the interval.

MI (p = 0.0001). Because peak enzyme levels are associated with infarct size,[20] we stratified patients according to peak SGOT level obtained, choosing 240 IU/liter as the cutoff point. We had previously found that this value separated patients into 2 groups with distinct in-hospital clinical courses.[7] All but 9 of the patients with non–Q-wave infarction had peak SGOT levels <240 IU/liter.

TABLE III Simple Unadjusted Chi Statistics for Cardiac Death in the First and Third Years After First Myocardial Infarction Based on Log Rank Test*

	First Year		Third Year	
Variable	Rank*	p	Rank	p
FIBFLUTTER	1	0.0001	8	0.3048
BUN >25	2	0.0001	17	0.9504
Cardiomegaly	3	0.0001	3	0.0208
LLDH	4	0.0014	6	0.1839
LSGOT	5	0.0028	15	0.5812
CHF	6	0.0046	9	0.3203
IVCD	7	0.0090	7	0.2871
PREVHT	8	0.0120†	18	0.9926
Age	9	0.0121	2	0.0205
Smoker	10	0.0264	10	0.4375
Q-wave infarction	11	0.0532	1	0.0203†
Caucasian	12	0.0547	16	0.6809
Sinus tachycardia	13	0.0582	12	0.5147
AV block	14	0.0835	13	0.5560
PVCS	15	0.0836	5	0.0807
SUPRAVB	16	0.1447	11	0.5029
Male	17	0.5163	14	0.5585
Diabetes	18	0.9429	4	0.0608

* Rank based on p values.
† negative correlation.
AV block = atrial ventricular block; BUN >25 = urea nitrogen, >25 mg/dl on hospital admission; CHF = congestive heart failure; FIBFLUTTER = atrial fibrillation or atrial flutter; IVCD = intraventricular conduction defect; LLDH = log 10 peak lactose dehydrogenase; LSGOT = log 10 peak glutamic oxalacetic transaminase (aspartate transaminase); PREVHT = a history of hypertension before initial infarction; PVCS = premature ventricular complexes; SUPRAVB = supraventricular beats.

Relation of type of infarction to new infarction within 60 days: Nine survivors of Q-wave MI (1.8%) had a second MI within 60 days of the index MI, and 3 of them died within 3 years. Seven patients with non–Q-wave MI (7.4%) had a new MI within 60 days of the first (p = 0.0136 relative to Q-wave MI) and 5 died within 3 years.

Effect of infarction type and estimated size on cardiac mortality: Figure 1 shows the cumulative cardiac survival in patients with Q-wave and non–Q-wave MI. The overall survival distributions of both groups of MI were not different. After stratifying the patients by peak SGOT, the differences in survival after each type of MI become clear (Table II, Fig. 2)(p = 0.007). (Among the 9 patients with non–Q-wave infarction and an SGOT level >240 IU/liter, there was only 1 death in the first years, so that all non–Q-wave MIs were combined into 1 group). Comparing cardiac mortality using the log rank test (Table II) over the first 3 years showed a marked difference in cardiac mortality rate (p = 0.0001) for the first 6 months among the 3

TABLE IV Final Parameter Estimates

Variable	Beta	Standard Error	Chi-Square	p Value
Cardiac Mortality in the First year				
FIBFLUTTER	1.068637	0.385205	7.70	0.0055
BUN >25 mg/dl	1.125076	0.385966	8.50	0.0036
Cardiomegaly	0.877607	0.350226	6.28	0.0122
LSGOT	1.603675	0.595372	7.26	0.0071
No previous hypertension	0.863448	0.327912	6.93	0.0085
Cardiac Mortality in the Third Year				
Age	0.052192	0.02164	5.81	0.0159
Non–Q-wave infarct	1.320417	0.441986	8.92	0.0028
LLDH	1.981166	0.90972	4.74	0.0294

Abbreviations as in Table III.

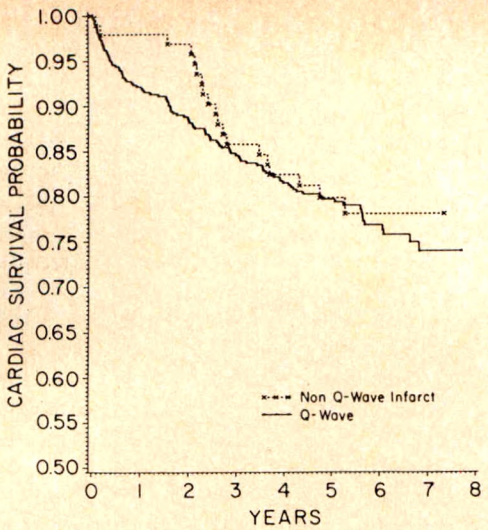

FIGURE 1. Cardiac survivorship for patients with Q-wave and non–Q-wave infarction.

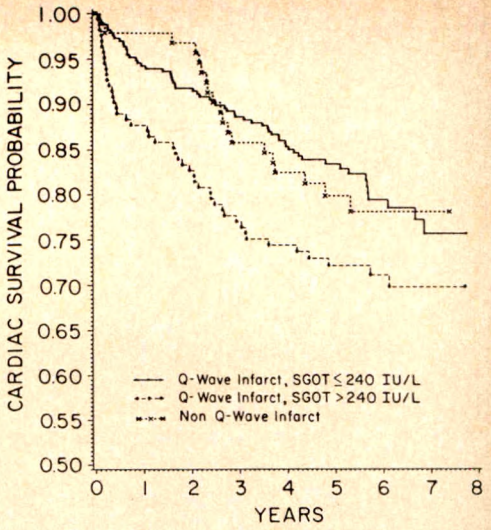

FIGURE 2. Cardiac survivorship of patients with Q-wave infarctic subgrouped by serum glutamic oxalacetic transaminase (SGOT) lev greater or less than 240 IU/liter compared with non–Q-wave infarctio Note the high early mortality in Q-wave infarctions with peak SGC >240 IU/liter and the high late mortality in non–Q-wave infarctions

groups. Patients with Q-wave MI and peak SGOT levels >240 IU/liter had a worse prognosis in the first 6 months than did those with either non–Q-wave or Q-wave MI with peak SGOT levels ≤240 IU/liter. From 6 months to 2 years after MI, survival in all 3 groups was similar. However, in the third year significantly more cardiac deaths occurred in patients with non–Q-wave MI (11.2% of the original number) than in those with Q-wave MI and SGOT levels ≤240 IU/liter (3.4%) or those with Q-wave MI with SGOT levels >240 IU/liter (6.8%). The survivorship curves (Fig. 2) demonstrate the different time course of survivorship for the different types of MI in the first 6 months and again in the thir year. The incidence of sudden death in these group generally paralleled the incidence of cardiac death fro all causes. Of the 50 sudden deaths in all patients in th first 3 years, 20 were unexpected and unwitnessed.

Contribution of other variables to mortality (Co model): We used a log rank test to assess the prognost significance of the demographic and clinical variable The univariate relations to cardiac death in the first an third year are shown in Table III. With the exceptio of cardiomegaly and age, most variables of significar

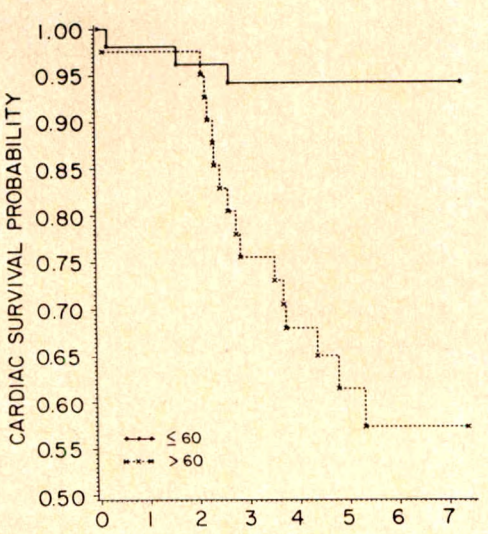

FIGURE 3. Cardiac survivorship in patients with non–Q-wave infarction subgrouped by age ≤60 or >60 years. There were 41 patients aged ≤60 years and 53 patients >60 years. Forty-five patients ≤60 years were followed up to death or to 4 years and 23 patients >60 were followed up 4 years. There were no deaths recorded in the ≤60 group after 3 years.

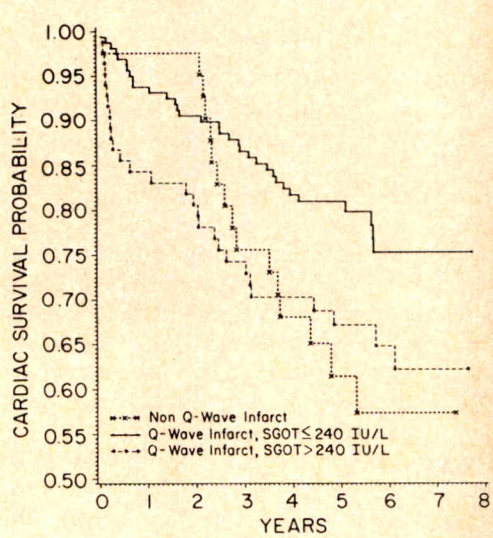

FIGURE 4. Cardiac survivorship in patients aged >60 years subgroupe by type of infarction and peak serum glutamic oxalacetic transaminas level (SGOT). The mortality of patients with non–Q-wave infarctio exceeds that of any other group 4 years after infarction.

prognostic value for death in the first year were not prognostic for death in the third year.

We used a stepwise procedure to fit a Cox model to assess the unique contribution to prognosis of a variable after considering the relation of other variables with stronger associations. The final result of the Cox model shows the independent predictors of death in the first and third years (Table IV). Most of the first year predictive variables can be associated with an extensive amount of infarcted myocardium. In contrast, in the third year, the type of MI (non–Q-wave) was the best independent predictor of cardiac mortality ($p = 0.0028$) and only the age and peak LDH level had additional predictive power (Table IV).

The possibility that the mortality of patients with non–Q-wave MI in the third year was due to an increased incidence of new infarctions occurring in the first 2 years was also examined, but no relationship was found. Of the 10 cardiac deaths in the third year, only 1 patient had a new MI in the first 2 years. Two patients had had a new MI 30 days before death and the remaining 7 patients did not have a documented new MI before death.

Importance of age: Increasing age was associated with a higher cardiac mortality in the patient population as a whole (Tables III and IV). When patients were grouped by both age (≤60 and 61 to 75 years) and type of MI, and Q-wave MI grouped by peak SGOT level, life-table curves showed that older patients had the highest cardiac mortality in both subgroups of Q-wave infarcts. This finding was especially marked in patients with non–Q-wave infarcts (Fig. 3, $p = 0.001$). Patients in both age groups had excellent survival in the first 2 years after infarction. Younger patients continued to have excellent survival, whereas older patients began to demonstrate a very high incidence of cardiac death after 2 years. By 4 years after infarction, cardiac survivorship in this group was the poorest of that in any group (Fig. 4).

Discussion

The terms *transmural infarction* and *nontransmural infarction* have been used for many years in the electrocardiographic classification of MI and continue to be used even though evidence indicates a poor correlation with pathologic findings.[23] MI without Q waves on the electrocardiogram may be transmural on pathologic examination and the reverse is also true.[24] In the present study, we showed that the distinction between Q-wave and non–Q-wave infarction is prognostically useful even though it may not be pathologically accurate.

We previously showed that in persons with a first infarction, those developing Q waves had a worse in-hospital prognosis than did patients who did not (11 versus 3%, $p = 0.007$).[7] Non–Q-wave infarctions released less enzyme and therefore were presumably smaller, which could account for the better in-hospital prognosis of these patients.

The present study shows that the long-term prognosis of patients after a first MI depends on the development or nondevelopment of Q waves, the peak level of enzymes released, and the patient's age. The largest division of our patients (the 56.6% in whom Q waves developed and who had an SGOT level <240 IU/liter) demonstrated a yearly cardiac mortality of 3.1% of the original survivors after 6 months, which continued at about the same rate thereafter. In that same group, patients aged >60 years had a slightly greater mortality (3.8% of the original survivors per year versus 2.9% of the original survivors per year in patients ≤60 years) ($p = 0.1629$). Patients with a presumably larger MI and Q-wave infarcts with SGOT levels >240 IU/liter had a very high mortality in the first 6 months after infarction (11%). However, after 6 months, cardiac mortality was steady at 3.8% of the original group per year thereafter, just slightly worse than the continuing mortality of the remainder of the patients with Q-wave MI and SGOT levels ≤240 IU/liter.

The experience of patients with non–Q-wave MI was totally different. For the first 2 years they experienced excellent survival (96.8%, a cardiac mortality of 1.6% per year), but beginning in the third year the older patients had a very high rate of cardiac death (12% of the original group per year) which 0ontinued for the duration of follow-up (Fig. 3). By the end of the fourth year, cardiac survival in this group was the lowest of that of any of the subgroups and remained so for the duration of follow-up (Fig. 4).

The survival curve for our patients with a first Q-wave MI is identical to that calculated from the data of Bland and White by Zumoff et al.[25] Cardiac mortality in these patients can be described by 2 superimposed survival curves, a fast component curve and a slow component curve. Our data suggest that the fast component or the worst mortality curve reflects the contribution of larger MIs, whereas the slower component mortality curve is a feature of all Q-wave MIs after 6 months. The non–Q-wave MI follows a totally different survival curve. Young patients have an excellent overall survivorship for at least 4 to 5 years after the initial MI, whereas older patients have an initially good survivorship but after 2 years have a very high cardiac mortality.

Parameters that defined the group at high risk in the first year after MI are similar to variables that influence acute in-hospital mortality[7,17–20] and reflect increased myocardial damage. The Q-wave feature of the MI was predictive of cardiac mortality simply because the Q-wave MI was generally larger than the non–Q-wave infarction.[7]

The mechanism of death beginning in the third year in older patients with non–Q-wave MI is not clear. Most cardiac deaths in our study were sudden, occurring within 1 hour of symptoms or unobserved. The role of ischemia in initiating what in most cases is probably an arrhythmic event is yet to be defined.[26] Hutter et al[6] reported a high incidence of angina (62%) in their patients with "nontransmural infarction" (46% of whom had a previous MI), but the relation between post-MI angina and subsequent mortality was not commented upon. Coronary angiography in patients with non–Q-wave MI has shown that the underlying coronary artery disease is as severe as that in patients with Q-wave MI,[27–29] but there is less ventricular damage. Older patients with non–Q-wave MI may have areas of

"jeopardized myocardium" [30] perfused by diseased vessels which may be at risk of sudden occlusion by thrombus or intimal hemorrhage[26] in the future. The higher incidence of a second MI within 60 days of the initial non–Q-wave infarction is consistent with this hypothesis.

We have shown that survival after a first MI is related to the appearance of Q waves. Early mortality (<6 months) reflects the amount of myocardial damage. Late mortality is not as strongly related to the amount of damage, but is strongly related to age >60 years and the absence of Q waves during the original MI. We have identified a group at special risk for mortality late after the first MI, that is, patients >60 years with non–Q-wave MI, and a low-risk group, that is, younger patients (≤60 years) with non–Q-wave infarcts. Procedures that attempt to delineate potentially ischemic myocardium in survivors of the index MI, such as standard stress testing, thallium stress testing, exercise radionuclide ejection fractions, and even coronary angiography, would appear indicated after most MIs, but the available data do not indicate whether this testing early after MI will identify persons at risk of dying after 2 years. Until more information is available, periodic reevaluation at intervals in these patients seems prudent, especially in older patients with non–Q-wave MI.

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Periods of Differing Mortality Distribution During The First Year After Acute Myocardial Infarction

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The mortality rate after acute myocardial infarction (AMI) has generally been modeled by a single exponential function. The present study was undertaken to determine, in 3 different populations, whether or not periods exist during the first year after AMI which have mortality distributions that differ from this pattern. The 3 patient populations included San Diego (346 patients, 71 deaths), Vancouver (704 patients, 146 deaths), and Copenhagen (1,140 patients, 262 deaths). Hospital admission was within 24 hours of the onset of symptoms, and patients dying within the first 24 hours after hospital admission or of noncardiac or unknown causes were not analyzed. The mortality between 2 and 21 days in the combined data base was 11.4% (range 10.9 to 11.7) and from 3 weeks to 1 year 10.5% (range 9.0 to 11.3). A high degree of similarity was noted among the shapes of the 3 survival curves. The hypothesis of an exponential mortality rate during the entire first year was rejected. Using a special statistic, changepoints at days 17, 23, and 24 in the 3 populations (21 days for the combined data base) were identified and used thereafter to divide the year into 2 separate periods of mortality within which exponentiality for the mortality rate was not rejected. The point by which exactly 50% of deaths had occurred was day 19, with 75% of deaths occurring by day 100. These data further define the natural history after AMI and indicate optimal follow-up periods for short- and longer-term management strategies based on risk assessment or trials of risk reduction after AMI.

Mortality after acute myocardial infarction (AMI) has often been modeled by an exponential distribution,[1,2] but detailed analysis of the shapes of survival curves has not been reported. If changepoints could be identified, differing mechanisms of mortality might be implied. Also, in developing management strategies based on risk assessment or for planning clinical trials of therapy after AMI, it would be advantageous if clear-cut follow-up intervals could be established that include most cardiac deaths. Studies following patients 2 to 10 years after AMI have shown that most deaths occur within the first several months,[3–10] whereas beyond the first year the mortality rate stays relatively constant at about 3 to 6% a year.[6–14]

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We investigated the appropriateness of an exponential model in 3 geographically distinct populations and considered the possibility that different periods of mortality could be characterized separately. Our goal was to determine whether generalizations can be made (despite variability among populations) concerning time intervals during which the majority of deaths occur in the first year after AMI.

Methods

Populations: Three geographically separate patient populations were used to investigate mortality during the first year after AMI. The population from Copenhagen, Denmark (CPH), consisted of 1,140 patients admitted to the hospital within 24 hours of the onset of symptoms. The diagnosis of AMI was established by at least 2 of the following criteria: (1) a history of characteristic chest pain, (2) electrocardiographic changes indicative of acute myocardial injury with subsequent evolution of a transmural infarction pattern, and (3) characteristic elevations of serum enzymes (creatine kinase, serum glutamic oxalacetic transaminase, or lactic dehydrogenase). Nontransmural infarction was diagnosed by typical S-T segment and T-wave changes accompanied by criteria 1 and 3.[15,16] For uniformity, the populations from Vancouver General Hospital (VANC) with 704 patients and the University of California, San Diego, Medical Center (UCSD) with 346

TABLE I Follow-Up and Mortality

	CPH		VANC		UCSD	
	n	%	n	%	n	%
Study period	1/77–1/80		11/77–1/80		8/69–6/79	
Patients (n)	1,140		704		346	
Follow-up (mo)						
6	1,140	100	696	99	334	97
12	1,140	100	658	94	321	93
Cardiac deaths						
Total (day 1 to 365)	364	32	179	25	92	25
Day 1	102	9	33	5	21	6
Day 2 to 15	117	10	66	9	35	10
Day 2 to 30	146	13	85	12	42	12
Day 2 to 365	262	23	146	21	71	21

CPH = Copenhagen; VANC = Vancouver General Hospital; UCSD = University of California, San Diego, Medical Center.

patients were extracted from their respective data bases to conform to these same criteria. For all 3 populations, patients meeting the foregoing criteria were consecutive.

Tables I and II show the characteristics of the 3 populations. The CPH patients were studied from January 1977 to January 1980, the VANC population over approximately the same period from November 1977 to January 1980. The UCSD population spanned nearly 10 years from August 1968 to June 1979. Follow-up for CPH was 100% and for VANC and UCSD about 93%. Of patients without a 1-year follow-up, 35 of 71 had their final contact during the last 2 months of the year. Patients dying from noncardiac (39) or unknown (21) causes were excluded from further analysis (Table I). All but 1 of the deaths from an unknown cause occurred in CPH where information was obtained from a national registry and the data were incomplete. Cardiac deaths were classified as cardiogenic shock, congestive heart failure, arrhythmia, myocardial rupture, new myocardial infarction, other cardiac (for example, during heart surgery) and sudden death (within 24 hours) presumed cardiac.

Mortality during the first 24 hours was highest for CPH (9%) patients compared with VANC (5%) and UCSD (6%) patients. However, when the period beginning with day 2 after admission through either 15 or 30 days was considered, mortality was more uniform at about 10% for 15 days and 12% for 30 days in each population. During the 364 days after the first day after admission, the mortality was 23% for CPH patients and 21% for both VANC and UCSD patients. Accordingly, we chose to analyze the deaths occurring during this period: CPH had 262 deaths, VANC 146 deaths, and UCSD 71 deaths.

The 3 populations were similar with respect to a number of characteristics recognized as indicative of prognosis (Table II). Heart failure was defined as the presence of rales above the scapula or positive signs of pulmonary venous congestion on chest X-ray during the hospital admission. The percentage of patients dying suddenly was 9% for CPH, 7% for VANC, and 11% for UCSD. A death was classified as sudden if it occurred within a short time (up to 24 hours) from the onset of the episode precipitating it. Documentation concerning the exact timing of events within the 24-hour period was not available. Factors in Table II were not statistically different among the 3 populations.

Other than routine therapy, very little secondary preventative measures were taken. Less than 5% of CPH patients, 18% of VANC patients, and 13% of UCSD patients were discharged on beta blocking drugs. Coronary artery bypass surgery was too rare to be noted. More recent data on patients from VANC (414) and UCSD (334) collected since 1980 indicate that 34% from VANC and 28% from UCSD are now discharged on beta blocking drug therapy. Also, 4% of VANC patients and 15% of UCSD patients have had coronary artery bypass surgery within 1 year after AMI. However, a survival analysis showed minor nonsignificant differences in 1-year survival rates between these new populations and the older data.

TABLE II Population Characteristics

	CPH	VANC	UCSD
Patients (n)	1,140	704	346
Age (yr, mean ± SD)	63 ± 12	65 ± 12	61 ± 13
Sex (% male)	72	70	72
Previous AMI (%)	31	20	26
Anterior location (%)	37	39	40
Complete heart block (%)	5	9	8
Congestive heart failure (%)	54	49	49
Sudden cardiac death from admission through 1 year (%)	9	7	11

AMI = acute myocardial infarction; SD = standard deviation; other abbreviations as in Table I.

Statistical methods: Survival curves for the 3 populations were compared with the Mantel-Cox statistic as calculated by the survival function program (P1L) provided in the BMDP Statistical Software Package.[17] This analysis took into account the exact time each patient was followed up to 365 days after admission to the hospital.

All the analyses to be described used only cardiac deaths during the period from day 2 through day 365. Because follow-up was close to 100%, especially during the first 6 months, no provision for lost patients was made in the analyses to be described.

First, a test was made to see if the distribution of deaths was exponential within each population separately and for the combined data base for the entire 364-day period. The statistic used is approximately normally distributed.* Another statistic based on the likelihood ratio was computed to determine a changepoint in time when the distribution of deaths became markedly less dense.* The changepoint determined from the combined data base was used to divide the year into 2 periods (early and late) and the analysis just described was repeated for both periods.

The distribution of deaths expressed as percent of patients still alive at a given point in time was fitted to an exponential curve using the nonlinear regression program (P3R) provided in the BMDP Statistical Software Package.[17] Fits were made for the entire 364-day period and for intervals resulting from the changepoint analysis.

* Details of the derivation and computation of these statistics can be obtained from the authors.

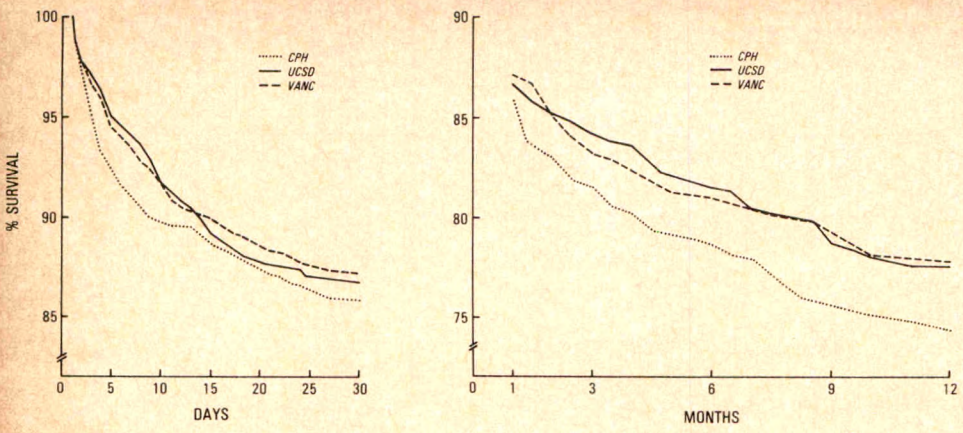

FIGURE 1. Left, percent survival from the end of day 1 (24 hours after admission) through day 30. **Right,** percent survival from the end of 1 month through 12 months. The curves are extensions of those in the left panel but are plotted on a different time scale. CPH = Copenhagen; UCSD = University of California, San Diego; VANC = Vancouver

TABLE III Hypothesis Test and Changepoints*

	CPH	VANC	UCSD	Combined
Days 2 to 365				
Exponentiality	9.90	7.17	5.02	13.05
Changepoint	24	23	17	21
Days 2 to 21				
Exponentiality	−1.48	−0.58	−1.33	0.17
Days 22 to 365				
Exponentiality	−0.30	−0.54	−1.61	−1.16

* Changepoint in days from admission. Combined = combined data base; other abbreviations as in Table I.

Results

Survival curves: The survival curves for the 3 populations are shown in Figure 1 and were not different statistically at the $\alpha < 0.05$ level.

Periods of differing mortality distributions: The values of the normally distributed test statistic are shown in Table III. A value of 1.96 for this statistic corresponds to an $\alpha < 0.05$ significance level. Thus, exponentiality for the entire 364-day period after the first day after hospital admission could be ruled out both within each individual population and within the combined population. The statistic for each analysis achieved an actual significance level of $\alpha < 0.0001$.

The changepoint (in days from hospital admission) determined by the likelihood ratio statistic was 24 days for CPH patients, 23 days for VANC patients, 17 days for UCSD patients, and 21 days for the combined data base. Using 21 days to establish 2 separate periods of mortality, the hypothesis of exponentiality could not be rejected for either the early or the late period (Table III).

The mortality within both the early and the late periods was remarkably similar within each population (Table IV). For the combined population, 11.4% of patients died from days 2 to day 21, representing over half (52%) of all deaths during the entire year, whereas during the late period, 10.5% of patients died (48% of deaths).

Separate exponential fits for the distribution of deaths in the early period (days 2 to 21) and in the late period (days 22 to 365) were much tighter than the overall fit obtained using all deaths in the 364-day period. The residual mean square error (an indicator of goodness of fit) summed for both curves in the 2-period analysis was dramatically reduced compared with that resulting from the fit for the entire period, the percent reduction being 76% for CPH patients, 86% for VANC patients, 96% for UCSD patients, and 85% for the combined data base. Figure 2 shows the natural logarithm of the actual survival data for each population. Up to 21 days, only every 10th death is plotted. The straight lines correspond to the fitted exponential curves for the entire 364-day period (single fit) and for the periods through (curve 1) and after (curve 2) day 21. These same data combined over all 3 populations are shown in Figure 2d, but only every 30th point was plotted up to day 21, every 10th point from day 21 through day 90, and every 5th point thereafter. The

TABLE IV Mortality During Early and Late Periods

	CPH		VANC		UCSD		Combined	
	n	%	n	%	n	%	n	%
Cardiac deaths								
Days 2 to 365	262	23	146	21	71	21	479	22
Mortality during								
Days 2 to 21	133	11.7	77	10.9	40	11.5	250	11.4
Days 22 to 365	129	11.3	69	9.8	31	9.0	229	10.5
Time (days) to								
50% of deaths	21		18		15		19	
75% of deaths	101		85		125		100	

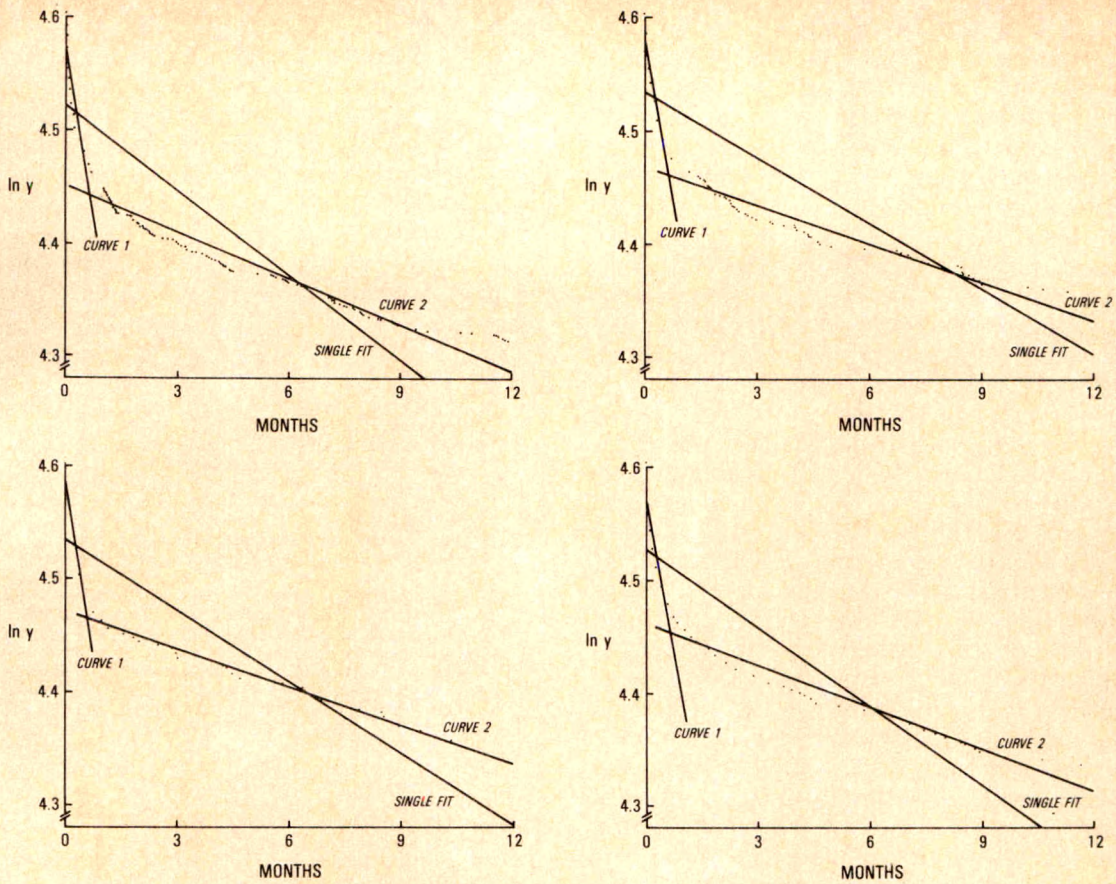

FIGURE 2. For each population, the natural logarithm of the percent of patients still alive at time t (ln y) is plotted against time in months. In the **top left** and **right** and **bottom left panels,** only every 10th raw data point up to 1 month is plotted (dots). In the **bottom right panel,** up to day 21 every 30th death is plotted, from day 21 to 90 every 10th death is plotted, and thereafter every 5th point is shown. The lines drawn correspond to the fitted exponential curves. Curve 1: fit for day 2 to 21; curve 2: fit for day 22 to 365. Single fit: fit for the entire 364-day period. **Top left,** Copenhagen; **top right,** Vancouver; **bottom left,** San Diego; **bottom right,** combined data base.

actual data in each population appeared to exhibit changepoints at the times calculated from the analysis (Table III).

Table IV gives the time in days by which 50 and 75% of the total deaths during the first year actually occurred in each population and in the combined data base. In the combined data base, 50% of deaths had occurred by day 19 (range days 15 to 21) and 75% had occurred by day 100 (range days 85 to 125).

Discussion

In 3 distinct populations, the 1-year mortality trends after the initial 24-hour period after hospital admission were found to be very similar. For each population, 2 distinct periods with differing exponential distributions of death could be clearly identified. Because the changepoints determined by the likelihood ratio method occurred within a fairly narrow range (17 to 24 days), the changepoint from the analysis of the combined data base (21 days) was used for the remainder of the analyses. None of the results differed substantially when the individual changepoints for each population were used within that population.

Appropriateness of the exponential model: Short-term survival up to 28 days after the onset of AMI has been modeled by a single exponential function for the purpose of studying pathogenic mechanisms and the effects of intensive coronary care.[1,18] One investigator suggested that an exponential survival function was not adequate because the hazard function was not constant but instead was decreasing.[19] The hazard function gives the probability that a patient will die in a short time, that is, 1 day, given that he has survived up to that time. To account for this decreasing force of mortality he chose to model his data with an appropriate Weibull distribution,[20] of which a special case is the exponential distribution. Although the Weibull distribution may have modeled adequately the decreasing force of mortality (in terms of goodness of fit), the decrease in the 3 populations studied appeared to occur rather abruptly, and the use of 2 simple exponentials fits the data well. The existence of a changepoint has clinical implications in that the mode and mechanism of death as well as the set of risk factors for mortality might differ substantially within each period.

The high mortality in CPH patients during the first 24 hours after admission could be due to patients in this population arriving at the hospital very soon after the onset of symptoms and dying shortly after arrival, whereas in the VANC or UCSD population, similar

atients may have died before hospitalization. For CPH atients the time from onset of symptoms to hospitalzation was available in only 813, with 101 of these patients arriving during the 24th hour. Omitting the 24th our group, mean arrival time after onset of symptoms as 4.5 ± 4.2 (standard deviation) hours, with over half f these patients arriving within 3 hours. For VANC atients the mean arrival time was 7.7 ± 5.4 hours and or UCSD patients 10.2 ± 6.3 hours. Neither the VANC or the UCSD population had a group of late arrivals. Omitting deaths occurring during the first 24-hour period after admission reduced the impact on the analysis f early hospital admission (especially for CPH).

If deaths occurring within the first 24 hours of hospital admission had been included, the results for ANC and UCSD patients would have been essentially he same. However, including the 102 such deaths in PH patients caused the hypothesis of exponentiality o be rejected for the early period. The changepoint etermined by the likelihood statistic computed for day through day 21 occurred at the end of day 1, and ortality from day 2 through day 21 did exhibit an exponential distribution. Even though the survival curve f CPH patients did not differ from that of UCSD and ANC patients (Fig. 1), the biphasic exponential fit was ot as good as that in the other 2 populations. For very arly interventions, such as thrombolysis,[21] candidates re generally accepted who arrive at the hospital within few hours of the onset of symptoms, and a separate nalysis of early arriving patients might reveal a omewhat different early survival pattern.[18]

For studying therapeutic interventions applicable to ost patients admitted within 24 hours after the onset f symptoms, our results should be relevant.[22] Such nterventions may seek to influence the acute course, eing instituted at about 24 hours after admission or at he time of hospital discharge to continue 4 to 12 onths. Between 21 and about 100 days, only 25% of irst year deaths will occur, with another 25% occurring hereafter (Table IV).

The identification in our study of 2 separate periods f risk should prove valuable in the design of intervention trials. For early interventions aimed at reducing arly death, a follow-up period of 3 weeks will include ost such deaths. For interventions instituted early, but aimed at reducing mortality well into the posthospital phase, a follow-up period of approximately 3.5 months will encompass 75% of cardiac deaths during the first year. To contain 90% of such deaths, follow-up would have to be well over 7 months, doubling the length and expense of the trial. For trials beginning at the time of hospital discharge it may be necessary to follow patients through the entire year to have a sufficient number of endpoints for analysis, because only about half of deaths during the first year occur after hospital discharge.

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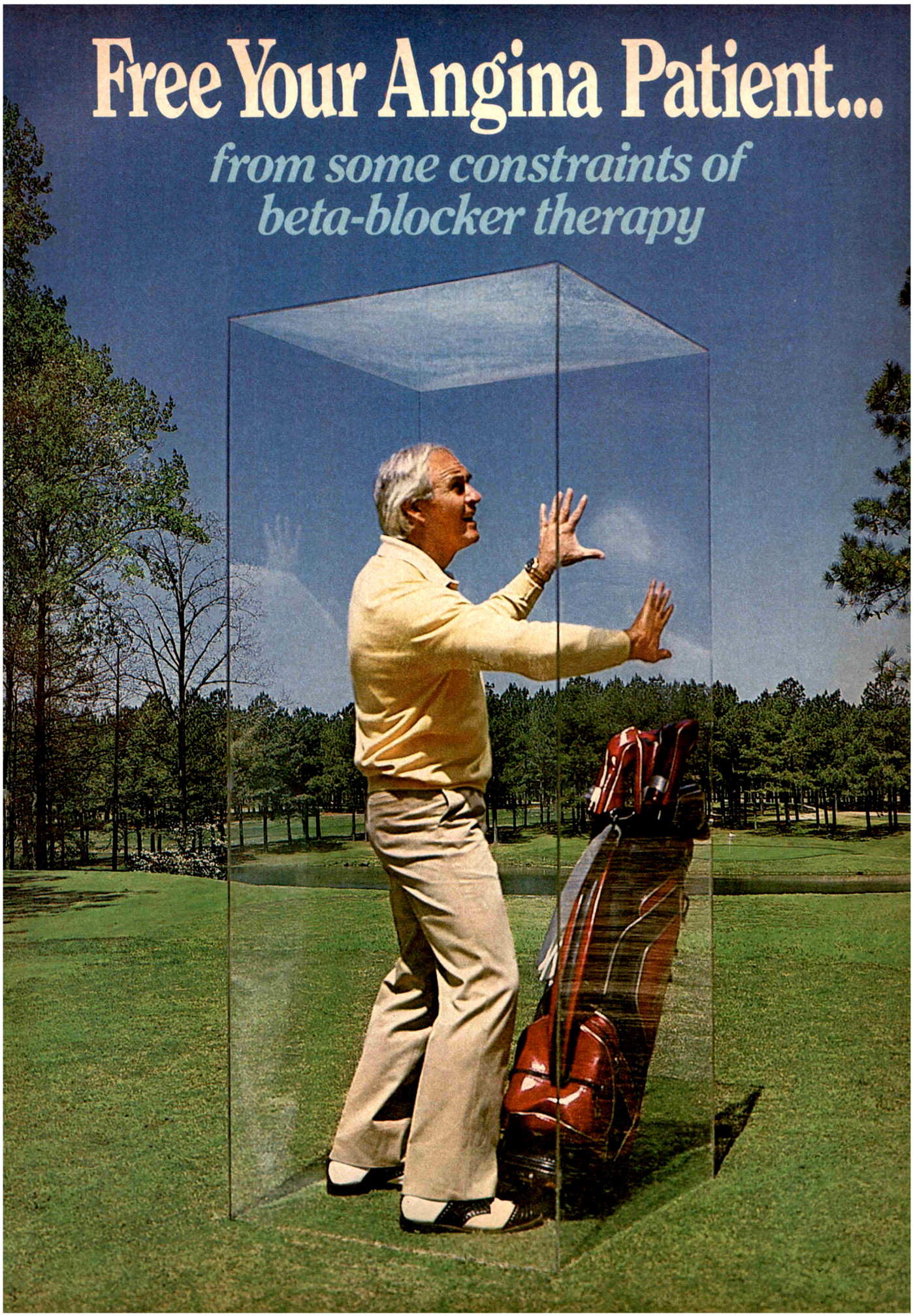
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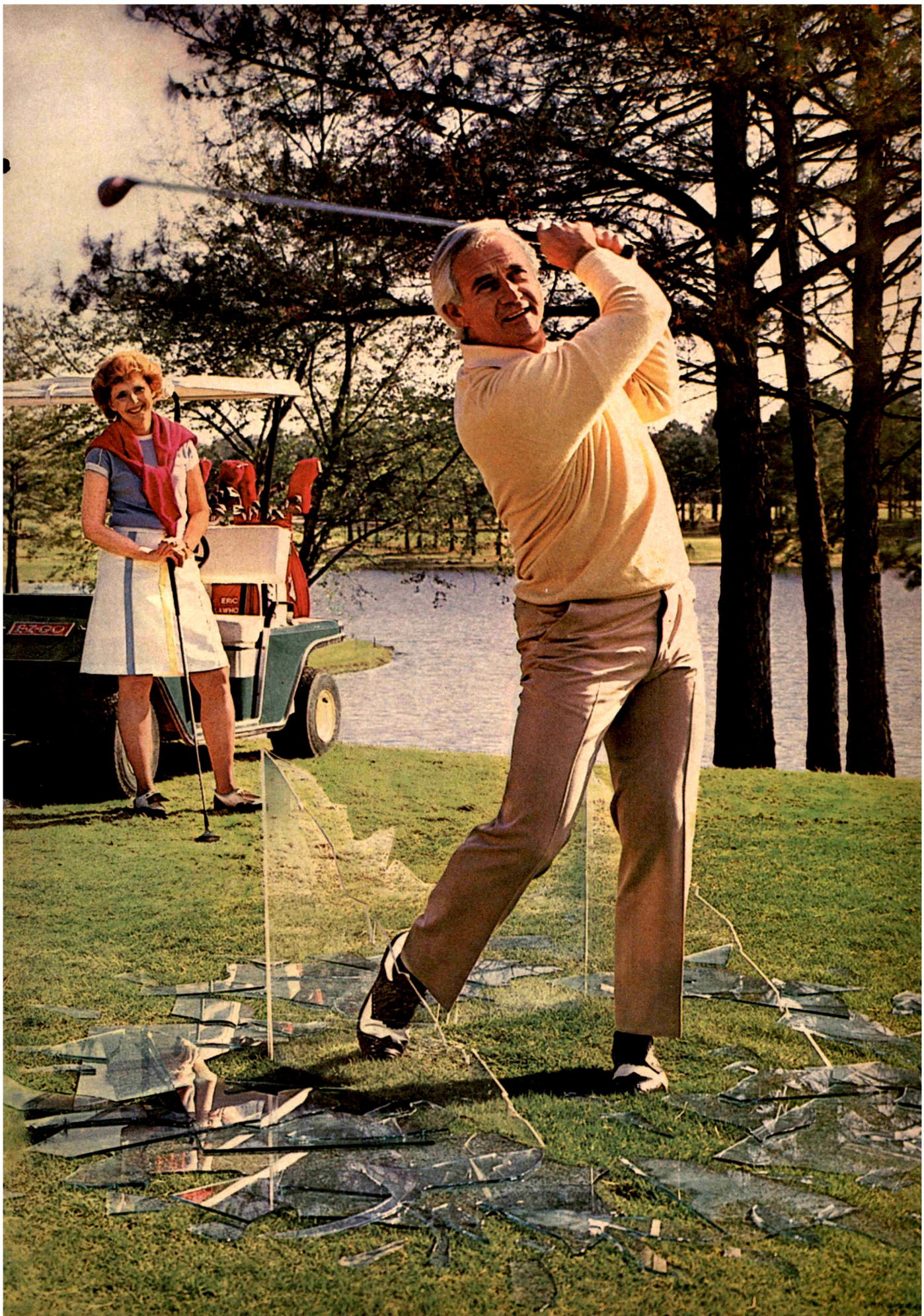
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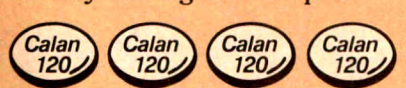

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Validation of Technetium-99m Stannous Pyrophosphate Myocardial Scintigraphy for Diagnosing Acute Myocardial Infarction More Than 48 Hours Old When Serum Creatine Kinase-MB Has Returned to Normal

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Determination of lactic dehydrogenase (LDH) isoenzymes is the current method of choice for diagnosing acute myocardial infarction (AMI) >48 hours old. However, other causes of enzyme elevation make the availability of an alternate method of diagnosis worthwhile. Accordingly, serial technetium-99m pyrophosphate scintigrams were obtained in 61 patients with transmural AMI and in 46 patients with subendocardial AMI. Imaging was performed in all 107 patients at the time creatine kinase isoenzyme (CK-MB) was present 37 ± 18 hours (range 12 to 72) after the onset of AMI, and at the time CK-MB was absent 106 ± 34 hours (range 48 to 168) after the onset of AMI. At the time CK-MB was absent, the sensitivity using either a regional or a diffuse positive scintigram was 95% (58 of 61 patients) for transmural AMI and 65% (30 of 46 patients) for subendocardial AMI. The sensitivity using a regional positive scintigram was 82% (50 of 61 patients) for transmural AMI and 37% (17 of 46 patients) for subendocardial AMI. The sensitivity using a high-grade regional positive scintigram was 36% (22 of 61 patients) for transmural AMI and 11% (5 of 46 patients) for subendocardial AMI. The specificity was 70% (143 of 204 patients) for either a regional or a diffuse abnormality, 92% (187 of 204 patients) for a regional abnormality, and 100% (204 of 204 patients) for a high-grade regional abnormality. Thus, pyrophosphate scintigraphy is useful in confirming the diagnosis of AMI, particularly transmural, >48 hours old and when CK-MB has returned to normal. A positive scintigram with a high-grade regional abnormality is specific for a recent AMI and may be contributory in establishing the diagnoses when LDH isoenzymes are inconclusive.

Since Bonte's pioneering work in 1974, technetium-99m stannous pyrophosphate myocardial scintigraphy has been widely used in diagnosing acute myocardial infarction (AMI).[1–8] If myocardial scintigrams are obtained between 24 and 72 hours after the onset of symptoms of AMI, >95% of patients with transmural AMI and from 38 to 92% of patients with subendocardial AMI will be detected.[1–9]

However, most patients with AMI can be diagnosed within 24 to 72 hours by serial electrocardiography and serum enzyme determinations at the time imaging with pyrophosphate is optimal. Pyrophosphate imaging in these cases would be unnecessary. Despite this limitation, pyrophosphate imaging has been useful in diagnosing perioperative AMI, localizing AMI (particularly right ventricular AMI), assessing the size of anterior transmural AMI, and providing prognostic information in patients during and after AMI, and in patients with unstable angina pectoris.[10–16]

It is frequently stated and commonly believed that the major role of pyrophosphate scintigraphy is diagnosing AMI in patients presenting >48 hours after onset of AMI when creatine kinase isoenzyme (CK-MB) has returned to normal.[17] In a limited number of patients studied by Parkey et al,[2] this would seem to be true although serial enzymes were not reported. Accordingly we performed a prospective, controlled study to determine the reliability of diagnosing AMI by technetium-99m pyrophosphate scintigraphy when serum CK-MB returned to normal. Serial pyrophosphate scintigrams

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nd enzymes were obtained in patients during the first days after the onset of AMI when serum CK-MB was resent, during 3 to 7 days after the onset of AMI when erum CK-MB was absent, and at hospital discharge.

Methods

From January 1980 to February 1981, 175 consecutive pa-ients admitted to the coronary care unit met our criteria for MI: (1) typical history of chest pain, (2) classic evolutionary lectrocardiographic changes, and (3) the presence of serum K-MB. AMI was localized by standard electrocardiographic riteria. Transmural AMI was defined by the presence on erial electrocardiograms of new Q waves with a duration of .04 second or more and amplitude >25% of the R wave in the ame lead, accompanied by evolutionary changes in the S-T egment and T wave. Subendocardial AMI was defined by the resence on serial electrocardiograms of new S-T segment hanges with or without T-wave abnormalities that persisted 24 hours.

Of the 175 patients, 68 (39%) were excluded from the study or the following reasons: (1) death within 96 hours after ospital admission (25 patients), (2) transthoracic cardio-ersion during coronary care unit stay (11 patients), or (3) ncomplete serial pyrophosphate studies. The patient did not ave a scintigram when serum CK-MB was present or when erum CK-MB was absent, or both, because of either clinical nstability or scintillation camera or radionuclide unavail-bility (29 patients), and refusal to participate in the study 3 patients).

The remaining 107 patients (61%) formed the patient opulation for the study. There were 106 men and 1 woman ith a mean age of 60.4 years (range 40 to 87). Sixty-one pa-ents had acute transmural AMI and 46 patients had acute ubendocardial AMI. Of the 61 patients with acute transmural MI, the AMI was anterior in 26 patients, inferior in 31, and nteral in 4. Of the 107 patients, 59 were Killip class I, 43 were illip class II, and 5 patients were Killip class III. Of the 107 atients, 39 (36%) had a history of previous AMI.

During the first 24 hours after hospital admission, all 107 atients had blood drawn for serum CK and CK-MB analysis very 8 hours, then daily for 7 days. In addition, all 107 pa-ents had blood drawn daily for serum LDH and hydrooxy-utyric dehydrogenase (HBD) analysis for 7 days after ad-nission. Serum CK-MB was determined by the cellulose ac-tate electrophoretic method. Significant CK-MB isoenzyme as reported present if more than a trace was detected by lectrophoresis.

After informed written consent, pyrophosphate imaging was erformed in all 107 patients at the time serum CK-MB was etected 37 ± 18 hours (range 12 to 72) after the onset of in-rction and at the time serum CK-MB was no longer detected 06 ± 34 hours (range 48 to 168) after the onset of AMI. Of the 07 patients, 97 (91%) had a follow-up scintigram before ospital discharge 21 ± 10 days after hospital admission. iming for pyrophosphate imaging was based on the results serum CK-MB analysis and scintillation camera and ra-onuclide availability. Imaging was performed within 3 hours CK-MB determinations. The initial scintigram was per-rmed within 72 hours of the onset of symptoms when serum K-MB was detected. It was attempted to obtain the second intigram on the first day in which CK-MB was no longer etectable. In some patients, the second scintigram was ob-ined 2 to 4 days after CK-MB had returned and remained ndetectable. None of the 107 patients had an episode of chest ain >15 minutes within 12 hours of the second scintigram. ecurrent AMI was excluded on clinical and electrocardio-aphic criteria before the follow-up scintigram.

Myocardial scintigrams were obtained 3 to 4 hours after the injection of 20 mCi of technetium-99m pyrophosphate, which contained <0.15 mg of tin. Chromatography was performed before each study to document the binding efficiency of the radiopharmaceutical. Myocardial scintigrams were recorded using a 37 PM tube, 11-inch standard field of view camera (420 Ohio Nuclear Portable or Pho Gamma V) fitted with a high resolution collimator.

Imaging was performed in anterior, 45° left anterior oblique, and left lateral views. Each view contained 400,000 counts with the 20% window and the photo-peak centered on 140 KeV. Serial studies on individual patients were performed with the same camera. Delayed imaging was performed at 4 hours in all patients suspected of having persistent blood pool activity.

Myocardial scintigrams were interpreted and graded in the following manner. The intensity of radioactivity in the area of the left ventricle was graded from 0 to 3+. Zero activity indicated no activity. An intensity of 1+ was assigned for activity less than that of the rib, 2+ for activity equal to or greater than rib activity, and 3+ for activity equal to or greater than sternal activity. A scintigram of 2+ or greater was considered positive. Our grading system differs from that proposed by Parkey et al[2] and Willerson et al.[3] A 2+ scintigram in our grading system corresponds to a 3+ scintigram in their system. This distinction is important because some investigators have considered a 2+ scintigram, according to the Parkey classification, as equivocal, but not a diagnostically positive scintigram.[18]

Myocardial scintigrams were also graded according to the distribution of activity. Regional uptake was assigned when activity could be localized to a discrete region of the left ventricle. Poorly localized activity was defined as diffuse uptake.

In comparing follow-up scintigrams with those obtained when serum CK-MB was detected, the following grading system was used. Follow-up scintigrams were considered improved if there was a decrease in the intensity of activity or if there was a change in the activity pattern from regional to diffuse. Follow-up scintigrams were considered worse if there was an increase in intensity of activity or a new regional abnormality pattern.

One hundred seven consecutive patients with unstable angina admitted to the coronary care unit during January 1980 to February 1981 who had a myocardial scintigram within 3 days after admission to the coronary care unit were the control patients. Unstable angina pectoris was defined as angina at rest lasting >15 minutes and no evidence of acute myocardial infarction after a 3-day observation period, as determined by serial electrocardiograms and serum enzyme determinations. None of the patients had new persistent S-T or T-wave changes or new Q waves on their electrocardiograms or an abnormal increase in serum CK, CK-MB isoenzyme, or serum HBD. These patients included 106 men and 1 woman, mean age 59.6 ± 10 years (range 30 to 82).

The myocardial scintigrams were interpreted by 2 experienced observers without knowledge of the patient's diagnosis or the results of enzyme determinations. When there was any disagreement in the interpretation of a scintigram, the lower grade was assigned. There was complete agreement between the observers in 90% of the scintigrams interpreted.

The data are presented as the means ±1 standard deviation. Sensitivity (%) was defined as the number of true-positive scintigrams divided by the number of true-positive plus false-negative results multiplied by 100. Specificity (%) was defined as the number of true-negative scintigrams divided by the number of true-negative plus false-positive results multiplied by 100. Chi-square analysis was used to test for significant differences.

TABLE I Characteristics of Technetium-99m Pyrophosphate Myocardial Scintigrams Obtained in Patients During Acute Myocardial Infarction, at Follow-up, and in the Control Group

		Positive Scintigrams				Negative Scintigrams	
	Patients	R_3	R_2	D_3	D_2	D_1	0
Acute phase: CK-MB present (12 to 72 hours after AMI)							
All patients with AMI	107	26	41	1	19	12	8
Transmural AMI	61	21	28	1	7	3	1
Anterior wall	26	12	11	0	3	0	0
Inferior wall	31	6	16	1	4	3	1
Lateral wall	4	3	1	0	0	0	0
Subendocardial AMI	46	5	13	0	12	9	7
Acute phase: CK-MB absent (48 to 168 hours after AMI)							
All patients with AMI	107	27	40	0	21	6	13
Transmural AMI	61	22	28	0	8	1	2
Anterior wall	26	10	13	0	1	1	1
Inferior wall	31	11	12	0	7	0	1
Lateral wall	4	1	3	0	0	0	0
Subendocardial AMI	46	5	12	0	13	5	11
Follow-up 21 ± 10 days after AMI							
All patients with AMI	97	0	10	0	27	39	21
Transmural AMI	54	0	7	0	11	25	11
Anterior wall	25	0	2	0	7	13	3
Inferior wall	25	0	4	0	3	11	7
Lateral wall	4	0	1	0	1	1	1
Subendocardial AMI	43	0	3	0	16	14	10
Controls	107	0	7	0	17	34	49

AMI = acute myocardial infarction; D_1 = diffuse 1+ activity; D_2 = diffuse 2+ activity; D_3 = diffuse 3+ activity; 0 = no activity; R_2 = regional 2+ activity; R_3 = regional 3+ activity.

Results

Scintigraphic findings at the time serum CK-MB was present (12 to 72 hours) after AMI (Table I): Fifty-seven of the 61 patients with transmural AMI (93%) had positive scintigrams with either a regional or a diffuse abnormality. Forty-nine of 61 patients with transmural AMI (80%) had positive scintigrams with a regional abnormality (Fig. 1).

Thirty of the 46 patients with subendocardial AMI (65%) had positive scintigrams with a regional or a diffuse abnormality. Of the 46 patients with subendocardial AMI, 18 (39%) had positive images with a regional abnormality.

At scintigraphy, the total serum CK was 1,160 ± 751 units/liter (range 243 to 4,120) for patients with transmural AMI and 488 ± 316 units/liter (range 194 to 1,201) for patients with subendocardial AMI. The normal range for total serum CK for our laboratory is 35 to 232 units/liter. Of the 46 patients with subendocardial AMI, 3 (6%) had total serum CK in the normal range when serum CK-MB was detected.

Scintigraphic findings at the time serum CK-MB was absent (48 to 168 hours) after AMI (Tables I and II): Fifty-eight of the 61 patients with transmural AMI (95%) had positive scintigrams with either a regional or a diffuse abnormality. Fifty of 61 patients with transmural AMI (82%) had positive scintigrams with a regional abnormality (Fig. 1).

Thirty of the 46 patients with subendocardial AMI (65%) had positive scintigrams with either a regional or a diffuse abnormality. Of the 46 patients with subendocardial AMI, 17 (37%) had a positive study with a regional abnormality.

At scintigraphy, the total serum CK was 150 ± 51.1 units/liter (range 55 to 292) for patients with transmural

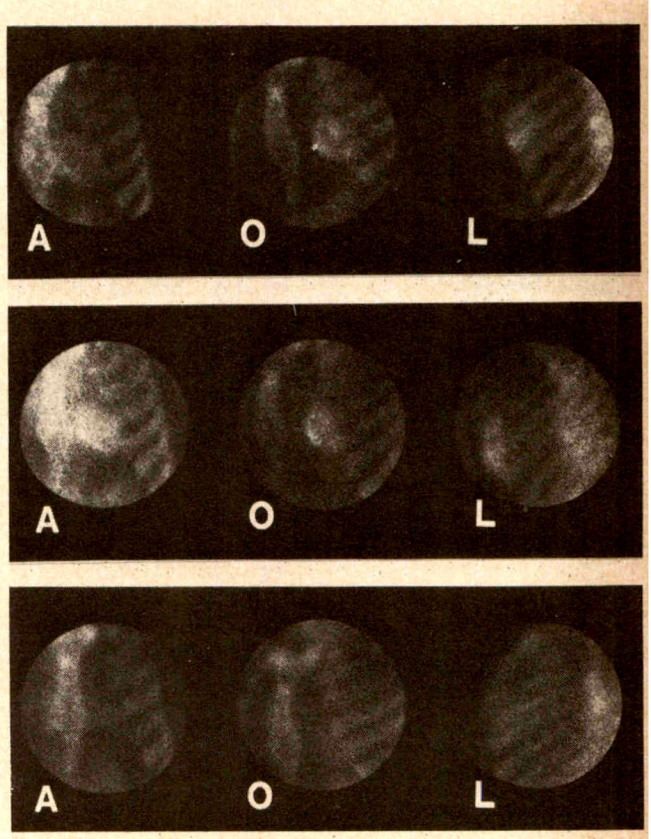


FIGURE 1. Upper panel, a 2+ regional abnormality (positive scintigram) in a patient with anterior wall acute myocardial infarction (AMI) 50 hours after the onset of AMI when serum CK-MB was present. **Middle panel,** a 3+ regional abnormality (positive scintigram) in the same patient 78 hours after the onset of AMI when serum CK-MB was absent. **Lower panel,** a negative scintigram at follow-up 15 days after the onset of AMI. A = anterior view; L = left lateral view; O = 45° left anterior oblique view.

ABLE II Correlation Between Scintigraphic Findings and Serum HBD in the 107 Patients 48 to 168 Hours After Acute Myocardial Infarction at the Time Serum CK-MB Was Absent

	Positive Scintigram					
	Regional or Diffuse Abnormality		Regional Abnormality		Elevated Serum HBD	
	n	%	n	%	n	%
ransmural AMI (61 patients)	58	95*,†	50	82*	55	90‡
ubendocardial AMI (46 patients)	30	65§	17	37	33	72¶
ll patients with AMI (107 patients)	88	82‡,‖	67	62	88	82‖

* p <0.001 when compared with subendocardial AMI.
† p <0.05 when compared with transmural AMI with a regional abnormality.
‡ p <0.05 when compared with subendocardial AMI.
§ p <0.01 when compared with subendocardial AMI with a regional abnormality.
¶ p <0.01 when compared with patients with subendocardial AMI with a positive scintigram with a regional abnormality.
‖ p <0.01 when compared with all patients with AMI with a regional abnormality.
AMI = acute myocardial infarction; HBD = hydrooxybutyric dehydrogenase.

MI and 143 ± 47.4 units/liter (range 36 to 269) for atients with subendocardial AMI. Six percent of pa- ients with transmural AMI (4 patients) and 6% of pa- ients with subendocardial AMI (3 patients) had slightly levated serum CK levels when CK-MB was unde- ected.

Figures 2 to 5 show the prevalence of positive scinti- rams in patients with transmural and subendocardial MI at the time serum CK-MB was present, at the time erum CK-MB was absent, and at follow-up.

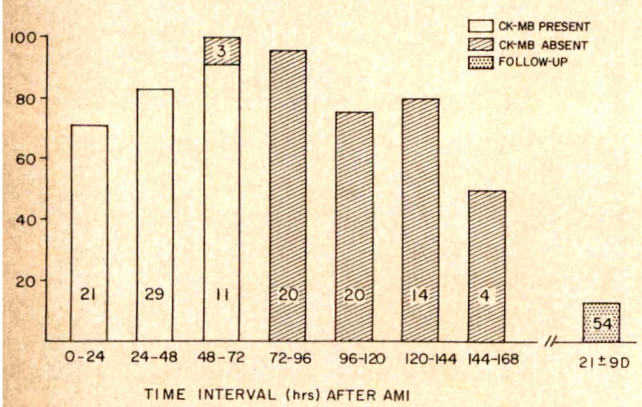
The peak incidence of positive scintigrams with a egional abnormality for transmural AMI occurred etween 48 and 96 hours after the onset of AMI. Ninety o 100% of patients with transmural AMI had positive tudies with a diffuse or regional pattern 12 to 120 hours fter the onset of AMI. The incidence of positive scin- igrams in patients with subendocardial AMI was ariable during the week after AMI.

The correlation between scintigraphic findings and erum HBD at the time serum CK-MB was absent is summarized in Table II. If the criterion for a positive scintigram was a regional abnormality, serum HBD was more sensitive than the scintigram for diagnosing subendocardial AMI when CK-MB was absent.

Of the 4 patients with inferior AMI with negative scintigrams when serum CK-MB was present, 3 had positive scintigrams when CK-MB was absent (Fig. 6). Similarly, 4 of the 16 patients with subendocardial AMI (25%) with negative scintigrams when CK-MB was present had positive scintigrams when CK-MB was absent. Thus, serial scintigraphy was able to diagnose AMI in 60 of 61 patients with transmural AMI (98%) and AMI in 34 of 46 patients with subendocardial AMI (74%).

Scintigraphic findings at follow-up (Table I): Of the 54 patients with transmural AMI who had follow-up scintigraphy, 7 (13%) had positive scintigrams with a 2+ regional abnormality at follow-up. Eighteen of the 54 patients (33%) had positive scintigrams with either a regional or a diffuse abnormality.

Of the 43 patients with subendocardial AMI, 3 (7%) had positive scintigrams with a 2+ regional abnormality



IGURE 2. Prevalence of positive scintigrams with a regional pattern patients with transmural acute myocardial infarction (AMI) evaluated ring the first week after the onset of AMI. The number of patients udied at each time interval is indicated in the bars. All intervals are gnificantly different compared with follow-up interval, p <0.001, cept interval 144 to 168 hours which is significantly different at p 0.05. Interval 72 to 96 hours is significantly different compared with terval 0 to 24 hours and interval 144 to 168 hours, p <0.05.

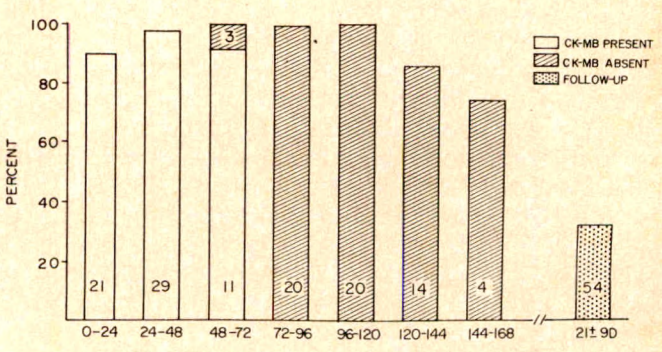


FIGURE 3. Prevalence of positive scintigrams with a regional or a diffuse pattern in patients with transmural acute myocardial infarction (AMI) evaluated during the first week after the onset of AMI. The number of patients studied at each time interval is indicated in the bars. All intervals are significantly different compared with follow-up interval, p <0.001, except interval 144 to 168 hours which is not significant. D = days; hrs = hours.

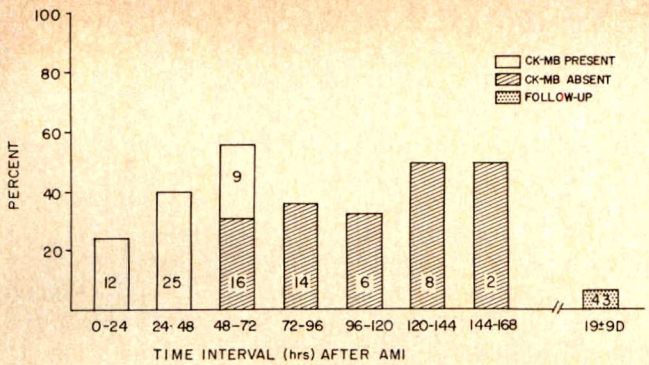


FIGURE 4. Prevalence of positive scintigrams with a regional pattern in patients with subendocardial acute myocardial infarction (AMI) evaluated during the first week after the onset of AMI. The number of patients studied at each time interval is indicated in the bars. Intervals: 48 to 72 hours, $p < 0.001$; 24 to 48 hours, 72 to 96 hours, 120 to 144 hours, $p < 0.01$; and 96 to 120 hours, 144 to 168 hours, $p < 0.05$, are significantly different compared with follow-up interval. Interval 0 to 24 hours is not significantly different compared with follow-up interval. D = days; hrs = hours.

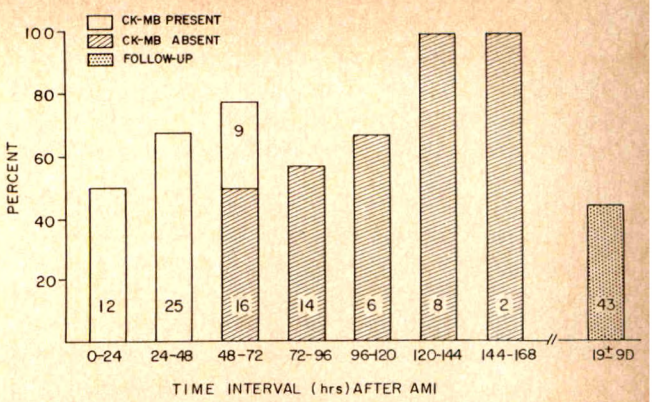


FIGURE 5. Prevalence of positive scintigrams with a regional or a diffuse pattern in subendocardial patients with acute myocardial infarction (AMI) evaluated during the first week after the onset of AMI. The number of patients studied at each time interval is indicated in the bars. Interval 120 to 144 hours is the only interval significantly different compared with the follow-up interval, $p < 0.01$. Interval 120 to 144 hours was significantly different compared with interval 0 to 24 hours and interval 72 to 96 hours, $p < 0.05$. D = days; hrs = hours.

at follow-up. Nineteen of these 43 patients (44%) had positive images with a regional or a diffuse abnormality at follow-up. None of the patients with transmural or subendocardial AMI had a positive scintigram with a 3+ abnormality.

Of the 30 patients with a history of previous AMI and a positive scintigram when CK-MB was present, 25 (83%) had an improved or negative scintigram at follow-up.

Of the 97 patients who had follow-up scintigraphy, 80 (82%) had positive scintigrams with a regional or a diffuse abnormality when serum CK-MB was absent. In comparing the scintigrams obtained at the time serum CK-MB was absent with those at follow-up, it is noteworthy that in 81% of cases, the scintigraphic abnormalities were either improved or negative (Fig. 1).

Control subjects (Table I): Of the 107 control patients, 7 (7%) had positive scintigrams with a 2+ regional abnormality. Twenty-four patients (22%) had positive scintigrams with a regional or a diffuse abnormality. None of the control patients had a 3+ regional abnormality.

The specificity of pyrophosphate scintigraphy for diagnosing AMI in this study was determined by combining the results of scintigraphy in the 97 patients with AMI at follow-up with the results obtained in the 107 control patients. The specificity was 70% (143 of 204 patients) for a 2+ abnormality (regional or diffuse), 92% (187 of 204 patients) for a 2+ regional abnormality, and 100% (204 of 204 patients) for a 3+ regional abnormality.

Discussion

Recent studies indicate that serum CK-MB isoenzyme determination is the most sensitive and specific method for diagnosing AMI.[9,19] However, it is of limited value for AMI occurring several days before hospital admission. For AMI >48 hours old, determination of serum LDH, LDH isoenzymes, or HBD activity is required to diagnose AMI.[20,21]

Separation and quantification of the isoenzymes of LDH increase specificity and accuracy for diagnosing AMI.[22] Vasudevan et al[21] showed that using the criterion of a reversal of LDH_1:LDH_2 >0.77 improved the sensitivity and specificity of LDH isoenzymes for diagnosing AMI. However, the sensitivity and specificity of the reversal of LDH_1:LDH_2 ratio for diagnosing AMI >48 hours old has not been completely evaluated. LDH_1 and LDH_2 isoenzymes are present in the kidneys, red blood cells, and brain and, to a lesser extent, in the lung.[22] Both hemolysis, such as occurs during simple withdrawal and handling of blood specimens, and renal disease can result in a false-positive LDH_1:LDH_2 pat-

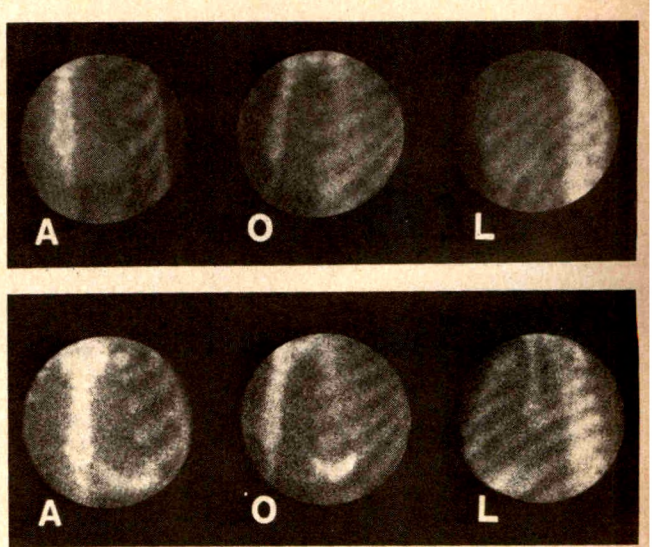


FIGURE 6. Upper panel, a diffuse 1+ abnormality (negative scintigram) in a patient with acute myocardial infarction (AMI) of the inferior wall 20 hours after the onset of AMI when serum CK-MB was present. **Lower panel,** a 3+ regional abnormality in the same patient 80 hours after the onset of AMI when serum CK-MB was absent. A = anterior view; L = left lateral view; O = 45° left anterior oblique view.

tern.[20] Moreover, a reversed ratio of LDH_1:LDH_2 is commonly found in young women, particularly during pregnancy.[23] Because of these problems with the current enzymatic methods, an alternative approach for diagnosing AMI that is >48 hours old would be worthwhile.

The major finding of the present study is that pyrophosphate myocardial scintigraphy is useful in diagnosing AMI, especially transmural AMI, during the first week after the onset of infarction when serum CK-MB is no longer detectable. Of the patients with transmural AMI, 95% had positive scintigrams with either a regional or a diffuse abnormality and 82% had positive scintigrams with a regional abnormality 3 to 7 days after the onset of AMI when serum CK-MB was no longer detectable. However, pyrophosphate myocardial scintigraphy is of limited value in diagnosing a 3- to 7-day old subendocardial AMI. Of patients with subendocardial AMI, 65% had positive scintigrams with a regional or diffuse abnormality and 37% had positive scintigrams with a regional abnormality when serum CK-MB was absent.

Previous animal and human studies have shown that pyrophosphate scintigraphy can detect myocardial necrosis within 12 hours after the onset of symptoms of AMI. Serial imaging indicates that the scintigrams become increasingly more positive 48 to 72 hours after the onset of AMI. There is then a gradual decrease in radioactivity in the infarcted area and the myocardial scintigram is usually negative by 2 weeks after the onset of AMI.[2,3,8,24] Myocardial scintigrams remain persistently positive in a minority of patients (usually a low-grade, diffuse abnormality) 3 to 6 months after AMI.[14,15] The suggested mechanisms for persistently positive scintigrams include left ventricular aneurysm and slow, on-going necrosis.[15,25]

The data from the present study support these experimental studies and human observations. The peak incidence of positive scintigrams with a regional abnormality occurred between 48 and 96 hours after the onset of AMI in patients with acute transmural AMI and between 24 and 72 hours after the onset of AMI in patients with subendocardial AMI. The later time for the appearance of a regional abnormality during transmural AMI may be due to the fact that a transmural AMI is more likely to be an occlusive AMI with later reperfusion.[26] Long et al[27] showed that during experimental AMI, early appearance of pyrophosphate uptake suggested a reperfusion AMI compared with later uptake in occlusive AMI.

The present study was not designed to compare pyrophosphate scintigraphy with serum enzymes such as LDH isoenzymes and HBD activity in diagnosing infarction that is several days old when serum CK-MB is no longer elevated. The sensitivity with either test was similar (pyrophosphate scintigraphy 82% and serum HBD activity 82%).

In our study, hospitalized patients with unstable angina were included in our control population because these patients would be most likely to have scintigraphy. Previous studies indicate that approximately one third of patients with unstable angina have abnormal scintigrams.[16,28] Histologic studies support the occurrence of myocardial necrosis associated with such abnormal scintigrams.[15] Accordingly, the specificity data refer to the routine clinical documentation of AMI by electrocardiogram and serum CK-MB. Specificity of pyrophosphate scintigraphy for diagnosing AMI is dependent on the nature of the patient population and the timing and sensitivity of the CK-MB assay.

In our study, a regional abnormality on pyrophosphate scintigraphy was specific for a recent AMI (92%). The specificity of a high-grade regional abnormality (localized activity greater than or equal to that in the sternum) was 100%. Whether pyrophosphate scintigraphy is more specific for diagnosing AMI when recent CK-MB is absent as compared with LDH isoenzymes will require further study. Pyrophosphate imaging may be helpful in confirming the diagnosis of recent AMI when LDH isoenzymes are equivocal or in clinical situations such as acute hemolysis when LDH isoenzymes are unreliable.

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Evaluation of Serial QRS Changes During Acute Inferior Myocardial Infarction Using a QRS Scoring System

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The evolution of changes in the QRS complex during the initial 3 days after the onset of an initial inferior myocardial infarction (MI) was studied in 82 consecutive patients. Each patient's standard 12-lead electrocardiogram was assigned points (a QRS score) according to the absolute duration of the Q and R waves and the amplitude ratios of R-to-Q and R-to-S waves. This QRS score has been demonstrated to correlate (r = 0.74) with the anatomic extent of single inferior MI. By this sytem, 43 patients (53% of the study group) had an initial electrocardiogram that registered a score of 0 and developed QRS points only after admission. The QRS scores of 18 additional patients (22% of the study group) changed after admission. Forty-nine score changes were noted on Day 2 and 18 on Day 3. All of these changes resulted in an increased QRS score.

Alteration of the QRS complex during initial inferior MI evolves over 2 to 3 days in many patients. There is a distinct pattern to this evolution, which results in sequential increases in a QRS score based upon electrocardiographic indicators of the extent of myocardial necrosis. This QRS scoring system might be applied to evaluate clinically interventions aimed at limiting the extent of necrosis in patients with initial acute inferior MI.

The effects of myocardial infarction (MI) on the scalar electrocardiogram have been recognized almost since the advent of electrocardiography.[1,2] In the QRS complex, R waves diminish and Q waves develop.[3–6] The temporal course of these changes has not been completely elucidated. In *Heart Disease*, a 1982 textbook of cardiovascular medicine,[7] QRS evolution is discussed only in reference to a hand-drawn diagram originally published by Lepeschkin in 1951.[8] This diagram suggests that acute QRS changes are limited to the first day after the onset of MI. Other reports have described changes in the QRS complex occurring over several days.[9,10] The present study examines the incidence, timing, and quantitative appearance of QRS changes during the first 3 days after the onset of initial, acute, inferior MI.

A recently developed[11,12] and simplified[13] QRS scoring system quantifies the QRS changes which occur as a result of MI. In the absence of other factors affecting the QRS complex, the magnitude of the QRS score correlates well with the size of both anterior[14] and inferior[15] MI determined at autopsy. It also correlates with decreases in left ventricular ejection fraction that result from MI.[16] The electrocardiograms of patients included in the present study were evaluated according to this QRS scoring system.

Methods

Patient population: During an 8-year period, 271 patients with acute inferior MI were admitted to the Duke University Medical Center Coronary Care Unit. Twelve-lead electrocardiograms were performed in these patients on admission and at least once daily for the first 3 hospital days. Serum enzymes, including creatine kinase (CK) and the nearly cardiac-specific isoenzyme CK-MB, were measured at varying intervals in all patients.

The 82 patients included in this study met the following criteria: (1) no MI by history or electrocardiogram, (2) acute

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TABLE I QRS Scoring System

Category	Lead	Duration (ms)	Amplitude Ratio (ms)	Maximum Points
Criterion for IMI required for inclusion in study	aVF	Q ≥ 30 (1)		1
Additional criteria for IMI	II	Q ≥ 40 (2)		
		Q ≥ 30 (1)		2
	aVF	Q ≥ 50 (3)	R/Q ≤ 1 (2)	
		Q ≥ 40 (2)	R/Q ≤ 2 (1)	4
Criteria for posterior involvement	V_1	R ≥ 50 (2)		
		R ≥ 40 (1)	R/S ≥ 1 (1)	3
	V_2	R ≥ 60 (2)		
		R ≥ 50 (1)	R/S ≥ 1.5 (1)	3
Criteria for apical involvement	V_5	Q ≥ 30 (1)	R/Q or R/S ≤ 1 (2)	
			R/Q or R/S ≤ 2 (1)	3
	V_6	Q ≥ 30 (1)	R/Q or R/S ≤ 1 (2)	
			R/Q or R/S ≤ 3 (1)	3
Criteria for anterior and lateral involvement used for exclusion from this study	I	Q ≥ 30 (1)	R/Q ≤ 1 (1)	2
	aVL	Q ≥ 30 (1)	R/Q ≤ 1 (1)	2
	V_1	Any Q (1)		1
	V_2	Any Q or R ≤ 10 (1)		1
	V_3	Any Q or R ≤ 20 (1)		1
	V_4	Q ≥ 20 (1)	R/Q or R/S ≤ 0.5 (2)	
			R/Q or R/S ≤ 1 (1)	3

IMI = inferior myocardial infarction.

infarction as indicated by elevation of S-T segments and the appearance of CK-MB in the serum sample, (3) definite inferior infarction as marked by the appearance of a Q wave ≥30 ms in lead aVF, (4) the absence of a concurrent anterior or lateral infarct (Table I), and (5) records of daily, scorable electrocardiograms for at least the first 3 hospital days. Electrocardiographic scorability required the absence of left and right ventricular hypertrophy, ventricular tachycardia, paced rhythms, left or right bundle branch block, and left anterior or posterior fascicular block.

Electrocardiogram and enzyme analysis: Electrocardiograms were recorded in the standard manner at 25 mm/s paper speed and 10 mm/mV amplitude. QRS complexes were measured with calipers and scored according to the system developed by Selvester et al[11,12] and simplified[13] and evaluated[14,15] by Wagner, Ideker, and their co-workers. Points were assigned according to the duration of Q and R waves and the amplitude ratios of R-to-Q or R-to-S waves (Table I). The amplitude ratios of R-to-Q waves were considered in a given lead only when a Q-wave duration criterion was satisfied in that lead.

QRS points achieved in leads II and aVF were attributed to inferior infarction; lead III is not considered in the QRS scoring system. When R-wave duration and R/S amplitude ratios were sufficiently increased to be assigned points in leads V_1, V_2, or both, the adjacent posterior myocardium was considered to be involved in the infarct. Adjacent apical involvement was identified by points in leads V_5 and V_6.

Although multiple electrocardiograms were performed in a single day on some patients, only 1 per day was consistently available in the population of this study. For that reason, only 1 QRS score per day could be applied in data analysis. When more than one electrocardiogram was available, the admission QRS score was used for Day 1 and the highest daily score was used for Days 2 and 3.

CK determinations were performed by the method of Rosalki[17] using the modified reagent substrate prepared by Eskalab. CK isoenzymes were identified using the Corning method with agarose electrophoresis.

Definitions: A *QRS change* refers to a score increase or decrease of ≥2 points compared with a previous observation. Minor fluctuations in R-wave and Q-wave dimensions resulted in frequent, transient, 1-point variations which were attributed to uncontrolled variables such as respiration, abdominal distention, and patient position. When sequential 1-point variations accrued to 2 points, thereby meeting the criterion for QRS change, the day on which the second point was observed was arbitrarily considered to be the day of QRS change.

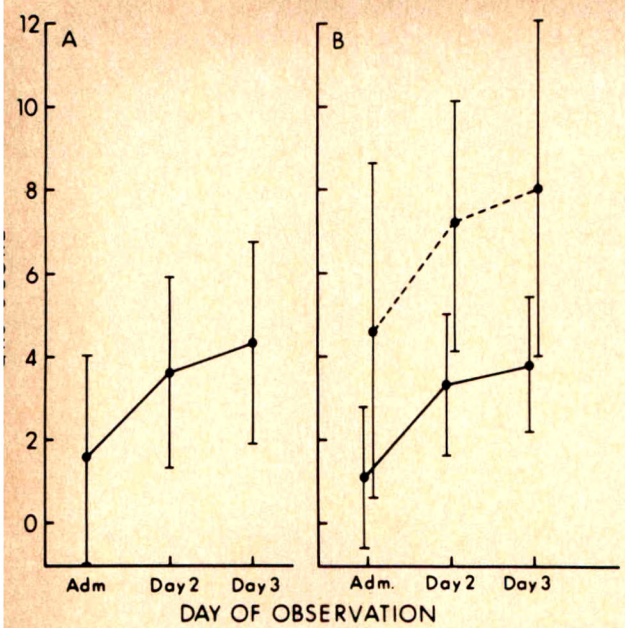
Day 1 began at the time of admission if CK-MB appeared in the serum sample within 24 hours. When no CK-MB appeared, the episode prompting admission was considered to have been unstable angina and Day 1 of the acute infarct was defined as beginning 12 hours before the first appearance of CK-MB. Day 1 always ended at 7:00 A.M. and every day thereafter lasted 24 hours.

Results

Eighty-two patients met the criteria for inclusion in this study, 72 of them with the QRS characteristics of inferior infarction alone. These patients' QRS changes occurred only in leads II and aVF, and they consisted of abnormal Q-wave durations and Q- to R-wave amplitude ratios (Table I). In 10 patients, these signs of inferior infarction were accompanied by changes in the chest leads, which indicated involvement of adjacent apical (1 patient), posterior (4 patients), or both apical and posterior areas of the myocardium (5 patients) (Table I).

Figure 1A illustrates the mean QRS scores observed during the first 3 hospital days. The 82 patients in the study had an average of 1.6 QRS points at admission, 3.8 points on Day 2, and 4.3 points on Day 3. Figure 1B provides the same information with the study group divided according to infarct location. The 10 patients with apical or posterior involvement or both had higher average QRS scores than those with only localized inferior infarcts (difference approximately 4 QRS points).

QRS score changes during the first 3 hospital days are summarized in Table II. Forty-three patients (53% of



GURE 1. Daily mean QRS scores (± 1 standard deviation). **A,** all atients in the study (n = 82). **B,** patients with localized inferior infarction **olid lines;** n = 72) compared with patients with apical or posterior volvement, or both, with inferior infarction (**dashed lines;** n = 10).

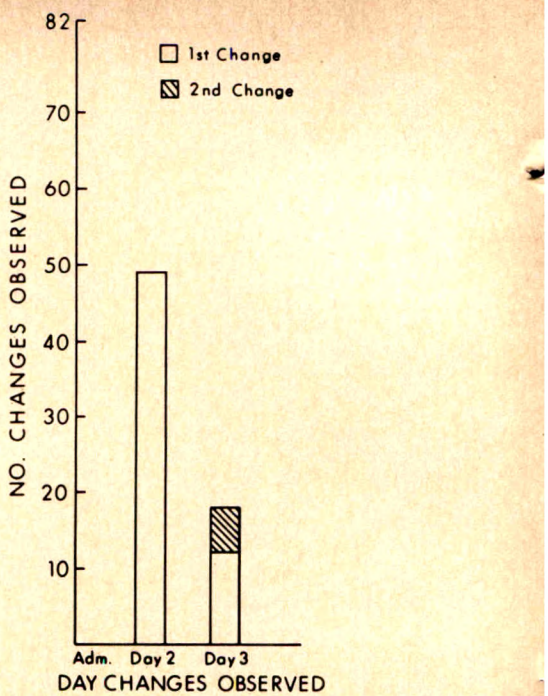


FIGURE 2. Days on which QRS changes were observed. Changes in relation to the admission QRS score are outlined; changes from the Day 2 score are shaded.

ıe study population) were admitted with a QRS score f 0. In 39 of these patients, the QRS score changed once fter admission; in 4 it changed twice. The other 39 atients in the study were admitted with ≥1 QRS oints. In 21 of them the QRS score did not change, in 3 it changed once, and in 2 it changed twice during the rst 3 hospital days. All 61 changes during this period sulted in increased QRS scores.

As Table III indicates, patients with adjacent apical r posterior infarct involvement, or both, were more likely than those with localized inferior infarcts to have been admitted with a QRS score >0. The number of patients in the apical or posterior groups, or both, was too small for consideration of statistical significance. The incidences of 0, 1, and 2 score changes were similar in the 2 groups of patients.

The timing of QRS score changes is summarized in Figure 2. The electrocardiograms of 49 patients indicated a change in QRS score between admission and Day 2. By Day 3, 12 more patients' scores had changed from admission. Six of the patients whose QRS scores had changed by Day 2, changed a second time by Day 3.

Electrocardiograms were available after Day 3 in a diminishing number of patients. Table IV shows that the incidence of change in QRS scores decreased markedly after Day 3, but a few changes in QRS scores were observed as late as Day 7. The score increases

ABLE II QRS Score Changes During the First 3 Hospital Days

	Admission Score = 0 (n = 43) (53%)	Admission Score >0 (n = 39) (47%)	Total (n = 82) (100%)
o change	. . .	21 (26%)	21 (26%)
ngle change	39 (48%)	16 (19%)	54 (67%)
vo changes	4 (5%)	2 (2%)	6 (7%)

ABLE III QRS Changes in Patients With and Without Posterior or Apical Involvement

	Inferior Infarct Only	Posterior and/or Apical Involvement
tients (n)	72	10
dmission score = 0	41 (57%)	2 (20%)
dmission score >0	31 (43%)	8 (80%)
o score change	18 (25%)	3 (30%)
ngle score change	50 (69%)	5 (50%)
vo score changes	4 (6%)	2 (20%)

TABLE IV Frequency of QRS Score Changes

Day	Patients With Data Available	Patients With Changes Observed (n)*	Patients With Data Available Observed to Change (%)
2	82	48	59
3	82	18	22
4	73	1	1
5	59	0	0
6	43	−1	2
7	35	3	9

* Positive numbers indicate QRS score increases; negative numbers indicate QRS score decreases.

noted after Day 3 all followed a period of 2 to 6 days without a score change. One patient's QRS score decreased on Day 6 from a higher score observed on Day 2.

Discussion

This study demonstrates that (1) changes in the QRS complex after the onset of MI often evolve over a longer period than that previously described, and (2) these changes follow a pattern. More than half of the patients studied were admitted before the development of abnormal Q waves. After admission, QRS changes were observed on Day 2 or 3 in most patients. All of the 61 observed changes during the first 3 days and 4 of the 5 late changes yielded increased QRS scores.

The appearance of the QRS complex after an infarct varies with the location,[18] the transmural depth,[8] and the subendocardial area[19] of the necrotic myocardium. The QRS scoring system devised by Selvester et al[11,12] and simplified by Wagner et al[13] quantifies the effects of these variables on the electrocardiogram. This scoring system correlates well with the size of anterior and inferior infarcts measured at autopsy when other factors such as previous infarcts, conduction disturbances, and ventricular hypertrophy are absent.[14,15]

In the present study, the QRS scoring system was used to analyze daily electrocardiograms of patients with acute inferior infarcts. The difference of at least 2 QRS points required for diagnosing a score change exceeds the observer variability previously documented in this laboratory.[13] Because all the observed changes during the first 3 days resulted in increased scores, and because the QRS score has been correlated with anatomic infarct size, it is likely that the observed increases indicate increasing necrosis.

Other explanations for QRS score changes cannot be excluded. One mechanism might be "infarct expansion," a process described by Hutchins and Bulkley,[20] in which the infarcted myocardial wall stretches and thins. This process potentially increases the proportion of infarcted myocardium exposed to surface electrodes, possibly altering the QRS complex. Such expansion, however, has been considered to become significant only by the fourth to fifth day after the onset of infarction. Almost all of the QRS changes observed in this study were noted during the second or third days. Moreover, infarct expansion has been observed much more frequently in patients with anterior infarcts; only 19% of the patients in the series of Hutchins and Bulkley[20] had inferior infarcts. On the basis of timing and location, therefore, it seems unlikely that many of the QRS changes observed in the present study resulted from infarct expansion.

Another possible cause of QRS change may be found in experimental studies which have identified increased extravascular fluid in infarcted myocardium.[21–23] Reimer and Jennings[21] have demonstrated in the canine model that this fluid can cause a 25% increase in infarct weight after 4 days. The fluid disappears after 28 days. Extravascular hemorrhage and edema might therefore have caused temporary QRS score increases during Days 5 to 7 of the present study, but very few changes were observed after Day 3. Extravascular fluid, like infarct expansion, occurs too late to correspond to the major period of QRS score change observed in the present study. Late electrocardiograms were unavailable, so resolution of QRS changes after 28 days could not be determined. A concurrent study in our laboratory, however, has documented minimal regression in QRS score during the initial 2 months after acute nonoperative infarcts.[24]

Ganz et al,[25] Beller et al,[26] and others[27,28] have performed experimental and clinical studies describing the sudden development of Q waves after myocardial reperfusion. These studies have shown that S-T segments diminish rapidly upon reperfusion, and Q waves concurrently increase. The investigators describing these events have suggested that Q waves may be "masked" by an injury current and "unmasked" by its resolution. In the present retrospective study, the relative timing of QRS change and S-T segment resolution could not be determined because of infrequent sampling. In experimental studies, however, Q waves have been shown to develop before injury currents resolve.[29] In addition, Q waves produced by coronary arterial occlusion were not diminished when reocclusion produced recurrent S-T segment elevation.[30] On the basis of these findings, it seems unlikely that QRS score changes result from injury current resolution.

The significance of QRS changes during the days after the onset of infarction remains uncertain. The changes probably reflect ongoing necrosis. Experimental studies in the canine model have yielded results which substantiate this possibility. A border zone of viable but ischemic tissue has been shown to exist within the perfusion field of an occluded vessel.[31–34] Lee et al[35] reported that this border zone may be of substantial size in man. Its source of perfusion is probably quite tenuous, being either collateral blood flow or flow through a highly stenosed epicardial vessel. In either circumstance, small disturbances in hemodynamic parameters may result in progressive myocardial necrosis during the early days after the onset of infarction. Unfavorable alterations in hemodynamic parameters may result in necrosis several days after the onset of infarction.

If ongoing necrosis is the determining factor in QRS score changes, such as those described in the present study, the infarction process may not be limited to a 24-hour period but may continue for 2 to 3 days in a significant proportion of patients. Moreover, among patients who are admitted with QRS scores of 0, the myocardium may not have undergone any necrosis before admission. Interventions initiated later than the first few hours after the onset of symptoms may have a greater potential for limiting infarct size than previously considered. Further investigation is required to determine the period in which such interventions can be effective. The standard 12-lead electrocardiogram may provide an important tool for evaluating interventions intended to limit infarct size, possibly with the goal of maintaining the minimal QRS score observed at the time of hospital admission.

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Coronary and Left Ventricular Angiographic Anatomy and Prognosis of Survivors of First Acute Myocardial Infarction

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To relate coronary anatomy and left ventricular function to prognosis, 197 of 269 consecutive survivors of a first myocardial infarction (MI) ≤60 years old underwent prospective cardiac catheterization a median of 2 weeks after admission and were followed up for a median of 24 months (range 12 to 61). Seventy-two patients were excluded from angiography because of early death (9), severe noncoronary disease (44), MI complications (6), or patient refusal (13). The prevalence of multivessel disease was low (30%) and unrelated to the site of MI or presence of Q waves but was increased in patients with previous angina pectoris ($p = 0.05$) or those in Killip class II or III ($p = 0.02$). There were only 8 deaths from heart disease. The survival rate at 12 months was 97 ± 1% and at 24 and 36 months, 95 ± 2%. Nineteen patients underwent coronary revascularization surgery. As the number of deaths was small, the differences in survival between patients with single or multivessel disease and normal or depressed ejection fractions failed to reach significance. Survivors of a first MI ≤60 years old have a low prevalence of multivessel disease and a good prognosis.

Beta-blockade therapy has been shown to reduce mortality in survivors of myocardial infarction (MI) and is accepted practice. MI is not, however, a homogeneous entity, and subsets of patients with varying prognoses can be identified, determined by age, number of MIs, degree of left ventricular (LV) dysfunction, and extent of coronary artery disease (CAD).[1–6] This study was designed to assess outcome in a common and sociologically important subset of patients: those ≤60 years old who have had their first MI.

Methods

Patient group: From October 1976 to June 1981, 269 consecutive patients ≤60 years old were admitted with their first MI: 197 underwent coronary arteriography at a median time of 2 weeks (range 10 days to 16 weeks) and form the study cohort (Table I). MI was defined from 2 of 3 criteria: (1) prolonged chest pain typical of myocardial ischemia; (2) development of pathologic Q waves on the electrocardiogram; and (3) an increase in serum creatine kinase activity to at least twice the upper limit of normal with an increase in creatine kinase-MB isoenzyme activity. Patients were not considered for study if they had had a previous documented MI, had Q waves diagnostic of a previous MI on the electrocardiogram, were transferred from another hospital because of complications of MI, or had undergone previous coronary artery surgery. Forty-four were excluded because of severe noncoronary disease: neurologic disease (5), severe systemic hypertension or renal disease, or both (7), severe peripheral vascular disease (6), respiratory disease (5), psychiatric disorder (4), severe diabetes mellitus (4), valvular heart disease (6), cardiomyopathy (2), malignancy (2), severe rheumatoid arthritis (1), blood dyscrasia (1), and recent motor vehicle accident (1). Five patients were excluded because of acute complications. Thirteen patients refused to participate in the study. Three of the patients who had been excluded from angiography and 9 of the eligible patients died in the hospital.

Clinical parameters: Clinical data were collected prospectively on each patient and entered into a computerized information system. This consisted of a detailed history, daily physical examination throughout the hospital stay, chest radiography, and electrocardiogram.

Clinical characteristics: The median age of the 197 patients was 51 years (range 27 to 60). One hundred sixty-five (84%) were men and 32 (16%) were women. Sixty-four patients (32%) had a history of angina pectoris for at least 10 days before admission. Electrocardiograms showed anterior MI in 96 patients (49%) and inferior MI in 99 (50%). Two patients had left bundle branch block at admission. Q waves developed in

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TABLE I Study Cohort

	Number
Patients admitted with first infarction	269
exclusions	
In-hospital deaths	9
Severe noncoronary disease	44
Complications precluding angiography	6
Patient refusal	13
Study patients	197

130 patients (66%). One hundred forty-nine patients were assessed as Killip class I (76%), 34 (17%) as class II and 14 (7%) as class III.

Catheterization and angiographic procedures: Coronary arteriography and left ventriculography were performed by the Sones and Judkins techniques. Cineangiograms were recorded in the right and left anterior oblique projections using axial views and read by 2 independent observers. LV ejection fraction (EF) was calculated for each patient using the area-length method.[7] In the right, left anterior descending and circumflex arteries, narrowing of >70% of the luminal diameter in any projection agreed by 2 observers was considered significant. Narrowing in large diagonal or obtuse marginal branches was classified as left anterior descending or circumflex disease, respectively. Left main coronary artery narrowing of >50% was regarded as significant. Only the most severe narrowing of each coronary artery was recorded and the patient classified as single-, 2-, or 3-vessel CAD.

Follow-up: After discharge, patients were followed up at 3, 6, and 12 months, and then annually to a median time of 24 months. The minimum follow-up time was 12 months. No attempt was made to influence management or drug therapy in this study. Patients were referred back to their own physician who supervised their medical care. The outcome was displayed on life tables with mean ± 1 standard error. Kaplan-Meier life table analysis[8] and log-rank testing[9] were used to compare outcome between groups. Patients who underwent surgery remained in the analysis up to that time and were then withdrawn from analysis alive.

Statistical analysis: Continuous data are expressed as mean ± 1 standard deviation and intergroup differences compared using the unpaired *t* test or 1-way analysis of variance when appropriate. Proportions are compared by the chi-square test with Yates' correction. A p value <0.05 was considered significant.

Results

Outcome: There were 10 deaths, of which 8 were due to heart disease. One death was due to ventricular fibrillation before discharge. Two deaths followed readmission with recurrent MI, 4 occurred suddenly out of the hospital and 1 was unwitnessed. The cumulative life-table survival for 197 patients (Fig. 1) was 97 ± 1% at 1 year, 95 ± 2% at 2 years, and 95 ± 2% at 3 years.

Relation of clinical findings to outcome: The mean age of the patients who died was 53 years. The following clinical variables were tested for their relationship to subsequent mortality: previous angina, infarct site, presence of Q waves, Killip class and development of ventricular tachycardia or fibrillation in the coronary care unit. None of these factors were significantly related to mortality.

Angiographic data: Single-vessel CAD was present in 123 patients (62%), 2-vessel CAD in 45 (23%), and 3-vessel CAD in 13 (7%). Sixteen (8%) had no vessel with >70% luminal diameter stenosis. Two patients had >50% stenosis of the left main coronary artery.

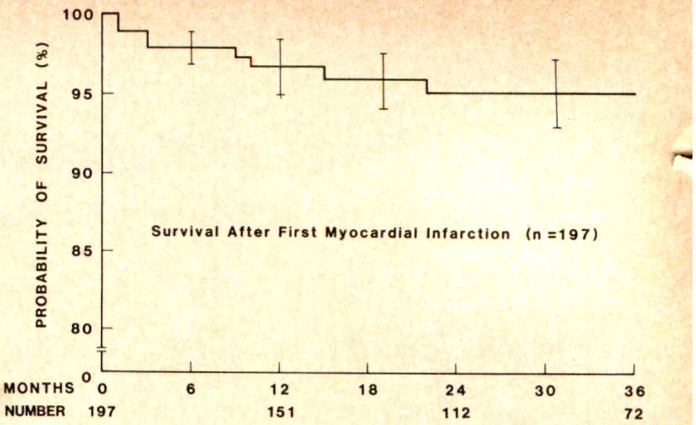

FIGURE 1. Cumulative life-table survival (± 1 standard error of the mean) for the total study group of 197 survivors of a first myocardial infarction aged ≤60 years.

The mean LVEF was 52 ± 13%. An EF ≥50% was found in 121 patients (61%), an EF of 40 to 49% in 45 patients (23%), an EF of 30 to 39% in 22 patients (11%), and an EF <30% in 9 patients (5%).

Relation of angiographic findings to outcome: The life-table survival of patients with single-vessel disease was 99 ± 1% at 1 year, 97 ± 2% at 2 and 3 years, and 97 ± 17% overall. There was no significant difference between the life-table survivals of patients with 2- and 3-vessel disease (chi-square = 0.003, difference not significant) and these were pooled as "multivessel disease." The life-table survival of patients with multivessel disease was 90 ± 5% at 1 year, 90 ± 6% at 2 years, 90 ± 7% at 3 years and 90 ± 28% overall (Fig. 2). The difference in life-table survival between patients with single and multivessel disease was not statistically significant ($0.14 > p > 0.025$).

The life-table survival of patients with LVEF ≥50% was 98 ± 14% and survival of those with EF <50% was 91 ± 28% ($0.1 > p > 0.05$) (Fig. 3).

Nineteen patients underwent coronary bypass surgery. Their mean age was 51 years. Eleven were in Killip class I, 6 in class II, and 2 in class III. Two had left main CAD, 5 had triple-vessel disease, 9 had double-, and 3 had single-vessel disease. The mean LVEF was 49 ± 14%. Both the patients with left main CAD and 2 with multivessel disease underwent surgery because of severe coronary disease despite only mild angina. Surgery was performed in 13 patients because of severe angina and 6 of these were operated on within 3 months of infarction. Two patients who had had cardiac failure associated with LV aneurysm underwent combined LV aneurysmectomy and coronary artery grafting.

Clinical findings and the prevalence of multivessel disease: The prevalence of multivessel CAD was significantly related to the presence of angina pectoris before infarction (Table II). Patients in Killip classes II and III had a higher incidence of multivessel disease than those in Killip class I (Table II). Although no patient <40 years old had 3-vessel CAD, the prevalence

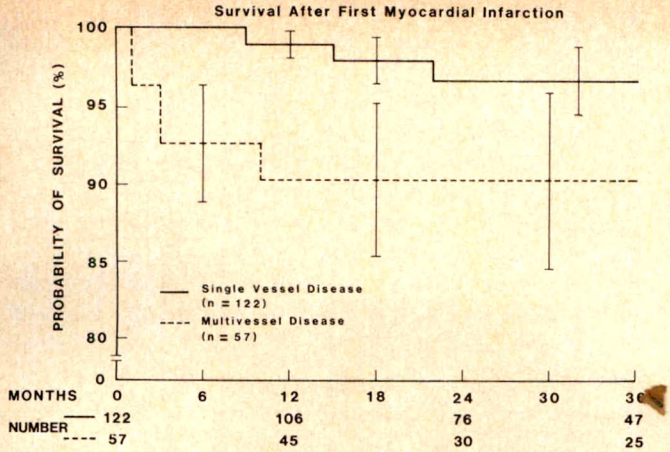

FIGURE 2. Life-table survival (±1 standard error of the mean) of patients with single- and multivessel disease.

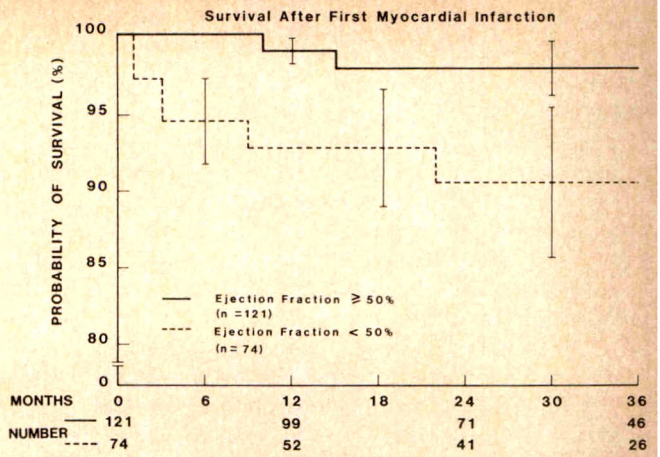

FIGURE 3. Life-table survival (±1 standard error of the mean) for patients with ejection fractions ≥50% and <50%.

of multivessel CAD was not significantly higher in patients >50 compared with those <50 years old. Neither the MI site nor the presence of Q waves altered the prevalence of multivessel disease.

Clinical findings and left ventricular ejection fraction: The mean LVEF decreased with increasing Killip class (Killip I, 55 ± 12%; Killip II, 47 ± 14%; and Killip III, 38 ± 14%) ($p < 0.01$) (Table III). Patients with Q-wave MI had a mean EF of 49 ± 13%, which was significantly lower than the 59 ± 11% mean EF of those with non–Q-wave MI ($p < 0.001$). LVEF was not related to the presence of angina before admission, age ≥50 years or <50 years, MI site or the occurrence of ventricular tachycardia, or ventricular fibrillation in the coronary care unit.

Discussion

This study describes the coronary anatomy and LV function and prognosis in 197 patients ≤60 years old who survived a first MI and underwent early, prospective cardiac catheterization.

There are 2 major findings in this study. First, there was a high (70%) prevalence of insignificant and single-vessel CAD. Second, the overall prognosis was good as only 8 patients died from heart disease during the follow-up period to a median time of 24 months.

The high prevalence of single-vessel or insignificant CAD results in part from the selection criteria for the study. Patients with previous MI and those >60 years old were excluded. Previous MI and advancing age have been shown to predict more severe CAD after MI.[10,11,13] Patients who were transferred from other hospitals because of complications were excluded. Patients with congestive heart failure, recurrent angina, and complex late arrhythmias have a high prevalence of multivessel CAD after MI.[10,11] If transferred patients are excluded, the patient population with acute MI tends to be from the surrounding geographic area. Because most hospitals that see and treat patients with MI receive patients from only the surrounding community, predictions of outcome should be made from this population rather than from the population referred and admitted to tertiary institutions.

A 5% annual mortality rate in males and a 7% rate in females <66 years old who had survived 30 days after an initial MI was reported from the community-based Framingham Study.[18] Recent studies report a better prognosis. Davis et al[2] found a 90 to 94% 3-year survival of patients <66 years old admitted to 2 community

TABLE II Clinical Findings and Prevalence of Multivessel Disease

Clinical Findings	n	Percent With MVD	p
Age ≤50 years	94	23	NS
Age >50 years	103	35	
Previous angina	133	39	0.05
No previous angina	64	25	
Killip II and III	48	44	0.02
Killip I	149	25	
Anterior MI	96	26	NS
Inferior MI	99	33	
Q-wave MI	129	31	NS
Non–Q-wave MI	66	24	

MI = myocardial infarction; MVD = multivessel disease; NS = not significant.

TABLE III Clinical Findings and Left Ventricular Ejection Fraction

Clinical Findings	LVEF (Mean ± SD)	p
Age ≤50 years	53 ± 14	NS
Age >50 years	52 ± 14	
Previous angina	53 ± 15	NS
No previous angina	52 ± 12	
Killip I	55 ± 12	
Killip II	47 ± 14	<0.01
Killip III	38 ± 14	
VT or VF in CCU	50 ± 17	NS
No VT or VF in CCU	53 ± 13	
Anterior MI	51 ± 14	NS
Inferior MI	54 ± 12	
Q-wave MI	49 ± 13	<0.001
Non–Q-wave MI	59 ± 11	

CCU = coronary care unit; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NS = not significant; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia.

hospitals with a first MI after high-risk patients had been excluded. Barnaby and Norris[19] reported a 4.5% death rate in the first year after first MI in men <60 years old, with a 3% annual mortality in years 2 to 4.

Because the death rate in our study is so low we have not been able to draw statistically significant conclusions about either clinical or angiographic predictors of mortality. The good prognosis reflects in part the low prevalence of multivessel CAD, which is a major determinant of death, both in patients with chronic CAD[4–6] and in survivors of MI.[12,13]

Other prospective studies of coronary anatomy after MI[10–13] have reported a higher prevalence of multivessel CAD. This ranged from 59% after first or subsequent MI[12] to 68% after first MI.[11] Most of these studies did not specify the proportion of referred, complicated patients, although De Feyter et al[13] excluded referred patients and found a 53% prevalence of multivessel CAD in a population of first MI survivors up to 65 years old.

Some investigators define 50% diameter stenosis as the lower limit for "significant" CAD,[10,12,13] whereas we and other investigators[11,14] accept >70% diameter stenosis. Analysis or our angiograms in terms of 50% diameter stenosis yields 3% insignificant disease, 52% single-vessel CAD, 30% double-vessel, and 16% triple-vessel disease.

The presence of multivessel CAD was poorly predicted by the infarct site, as reported by other prospective studies of coronary anatomy after infarction.[10,11] Several nonprospective series[14–16] have reported a higher prevalence of multivessel disease after inferior MI, but included patients referred for angiography because of post-MI angina. However, De Feyter et al,[13] in their prospective study, reported a significantly higher prevalence of multivessel disease after first inferior MI than after anterior MI.

A history of angina before or cardiac failure after MI increased the probability of multivessel disease, as has previously been reported,[10,11,15] but neither was a sensitive predictor of anatomy.

The exclusion of 44 patients with serious noncoronary conditions, especially hypertension, renal failure, or diabetes, may have reduced the prevalence of multivessel disease and, consequently, reduced the cardiac mortality in the study population.

The outcome of our patients may have been influenced by the current attitudes to management of CAD, whereas no attempt was made to influence the physicians who cared for the patients in this study. Nineteen patients underwent coronary surgery, 2 with left main CAD and 2 others because of severe coronary lesions but few symptoms. Thirteen underwent surgery because of severe angina pectoris and 2 because of LV aneurysms with associated heart failure. Forty-five percent received beta-blocking drugs after discharge. Beta-blocking drugs may have influenced the outcome[17,20,21] but, in the timolol trial[21] there was no reduction in mortality in uncomplicated survivors of first MI who received drug treatment. Although both the surgical and medical therapy may have altered the outcome in these patients, their contribution cannot be determined; nevertheless they reflect the usual management of patients after MI today.

The present study suggests that patients ≤60 years who survive their first MI have a low prevalence of multivessel CAD and a good prognosis.

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Coronary Arterial Aneurysm Formation After Balloon Angioplasty

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The mechanism of coronary stenosis dilatation by percutaneous transluminal coronary angioplasty (PTCA) is incompletely understood. Five men who developed coronary arterial aneurysms at the site of PTCA are described. All patients were in New York Heart Association functional class III or IV at the time of PTCA. In 2 patients acute myocardial infarction was evolving and both had acute coronary occlusion. The other 3 patients had angiographic evidence of intimal disruption or acute coronary reocclusion as a result of PTCA, one of whom had undergone emergency coronary artery bypass grafting. Three patients received intracoronary streptokinase during PTCA. One patient was asymptomatic and 4 were symptomatic when the aneurysms were identified between 11 days and 4 months after PTCA. Other than the complex course and anatomy of these patients before and immediately after PTCA, no other features distinguished them from others undergoing this procedure.

The improvement in coronary artery size after percutaneous transluminal coronary angioplasty (PTCA) is presumably due to some degree of plaque compression-disruption and injury to various layers of the vessel wall.[1] Cadaver and animal studies suggest that acute effects of dilatation involve intimal and medial layers.[1–6] Limited information is available, however, regarding coronary artery remodeling over time as a result of this "controlled" injury. Coronary artery occlusion and dissection-disruption immediately after PTCA have been reported, but to our knowledge, aneurysms at the site have not been described.[7] This study describes formation of coronary arterial aneurysm after PTCA in 5 patients.

Methods

Patients: Five men who underwent PTCA for angina were studied. All had important stenoses at angiography that persisted after administration of nitroglycerin. Coronary stenosis was quantified and PTCA was done as described by Grüntzig et al,[8] with modifications as noted. Appropriately sized guiding and dilatation catheters were chosen based on vessel size and location of stenosis. Heparin, nitroglycerin, low-molecular-weight dextran and nifedipine (except in Patient 1) were administered during PTCA; aspirin, dipyridamole, and long-acting nitrates were given after the procedure. During the 3-year period when these patients were seen, more than 450 PTCA procedures were done at our institution and more than 200 were followed up with repeat angiography. All patients gave informed consent and investigational aspects of PTCA were approved by appropriate institutional review committees. Pertinent features of these cases are summarized in Table I.

Patient 1 had angina for 4 years. After undergoing left anterior descending artery (LAD) bypass surgery, he did well for >4 years and then developed unstable angina. Four hours after he had an acute inferior myocardial infarction, the right coronary artery was found totally obstructed after intracoronary nitroglycerin (Fig. 1). After guide wire recanalization without difficulty, subtotal (99%) occlusion persisted. Streptokinase (122,000 U) was administered over 56 minutes into the right coronary artery but 95% occlusion persisted. PTCA was done without difficulty (Table I), but 50% stenosis remained without angiographic evidence for coronary dissection or aneurysm (Fig. 1). At elective follow-up study performed 2 months later, the patient was asymptomatic, with normal left ventricular hemodynamic function, minimal inferior hypokinesia greatly improved, and an aneurysm localized to the dilatation site (Fig. 1).

Patient 2 had exertional angina for 9 months which increased in frequency and severity over several weeks. He had obstruction only in the mid-LAD (Fig. 2). After PTCA, performed without difficulty, minimal residual stenosis persisted (Table I) with a short linear luminal defect at the dilatation

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TABLE I Summary of Pertinent Findings at Catheterization

Case	Age (yr)	Coronary Angiographic Findings (% Diameter Reduction)					Pressure Findings		Other Findings			
		Before PTCA		Immediately After PTCA		Later Location of Aneurysm	Stenosis Pressure Gradient (mm Hg)	Maximal Inflation Pressure (atm)	Guiding Catheter	Dilating Catheter	Additional Drug Treatment*	MISC
		RCA	LAD	RCA	LAD							
1	57	95	. . .	50	. . .	RCA	50	7	9FR4	J 20-30	Streptokinase, 122,000 U	AMI 4 hours before PTCA; wire recanalization
2	61	. . .	80	. . .	20	LAD	56	7	9FL4G	DG 20-30 DJ 20-30	Nifedipine	CABG at 4 mo
3	56	. . .	75	. . .	10	LAD	16	5	9FL4G	DJ 20-30	Nifedipine Streptokinase, 15,000 U	. . .
4	53	. . .	90	. . .	Double lumen	LAD	75	6.5	9FL4G	G20-30 DG 20-20 DG 20-30	Nifedipine	Emergency CABG
5	65	. . .	100	. . .	Double lumen	LAD	50	6.5	8FL4G	G 20-30	Nifedipine Streptokinase, 60,000 U	AMI 5 hours before PTCA

* All patients received heparin, nitroglycerin, and low-molecular-weight dextran.
AMI = acute myocardial infarction; atm = atmospheres; CABG = coronary artery bypass grafting; LAD = left anterior descending artery; MISC = miscellaneous; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

site. Within 4 months, angina developed and increased in severity. The LAD now had sequential stenoses with an aneurysm at the dilatation site (Fig. 2). Bypass surgery was performed but the patient required continued antianginal medication.

Patient 3 had an anterior myocardial infarction and developed progressive angina over the next year. He had proximal LAD stenosis involving a large diagonal branch (Fig. 3). After PTCA, performed without difficulty, minor irregularities were seen at the area of previous stenosis with slow contrast filling of the diagonal branch. Because these irregularities suggested thrombus, streptokinase (15,000 U) was injected into the LAD. He did well, but after 4 months exertional angina recurred. The LAD had irregularity at the dilatation site and an aneurysm proximal to the origin of the previously involved diagonal branch. Slow contrast filling of the diagonal branch with narrowing proximally persisted (Fig. 3).

Patient 4 had recent onset angina, S-T segment depression at low-level exercise, and 90% proximal LAD stenosis (Table I). At PTCA, difficulty advancing the balloon across the stenosis occurred, so the catheter was withdrawn. Angina developed and decreased contrast flow in the LAD appeared and persisted after intracoronary nitroglycerin was given. A smaller balloon catheter (DG20-20) was advanced across the stenosis without difficulty. After 4 inflations it was replaced with a larger (DG20-30) catheter. Multiple inflations decreased the pressure gradient and severity of stenosis but a double lumen and poor distal contrast flow resulted. Because of persisting angina with S-T and T-wave changes, an intraaortic balloon pump was inserted and bypass surgery performed using the internal mammary artery. No evidence for perioperative myocardial infarction evolved. On the third postoperative day, 2 episodes of angina occurred. Eleven days postoperatively the mammary graft to the mid-LAD was patent, but proximally an aneurysm was localized to the site of the LAD angioplasty and total occlusion had developed just distal to the aneurysm.

Patient 5, with angina rapidly accelerating in frequency and severity over 2 weeks, had long 95% proximal and 50% mid-LAD obstructions. The next day, 5 hours after the onset of an acute anterior myocardial infarction, total LAD occlusion was found at the site of previously demonstrated proximal stenosis. After intracoronary administration of streptokinase (60,000 U), the LAD reopened with 75% residual stenosis. After PTCA, the LAD was widely patent with a linear luminal defect localized to the dilatation site, and a routine electrocardiogram taken in the coronary care unit showed anterior-lead S-T-segment elevation. Repeat angiography now revealed total LAD occlusion and a 3F Teflon® catheter was advanced across the occlusion without difficulty. Intracoronary nitroglycerin and streptokinase reopened the LAD artery, but enzyme and electrocardiographic changes of anterior myocardial infarction evolved. Two weeks later 30% proximal LAD occlusion at the dilatation site and 2 other areas of approximately 40% occlusion were present. At the dilatation site there was evidence for dissection but not aneurysm. Angina recurred after discharge and 3 months later angiography revealed that the 30% proximal LAD occlusion was unchanged. Distal to this stenosis, at the previous dilatation site, there was a long (approximately 2 cm by 5 mm) aneurysm followed by 50% stenosis (Table I).

Clinical and angiographic characteristics: Other than severe symptoms related to coronary artery disease, there were no clinical factors such as hypertension, diabetes, and other conditions that made this particular group different from other patients who had undergone PTCA as represented by the Registry of the National Heart, Lung, and Blood Institute.[9] None of these patients had distal stenosis, so the dilating

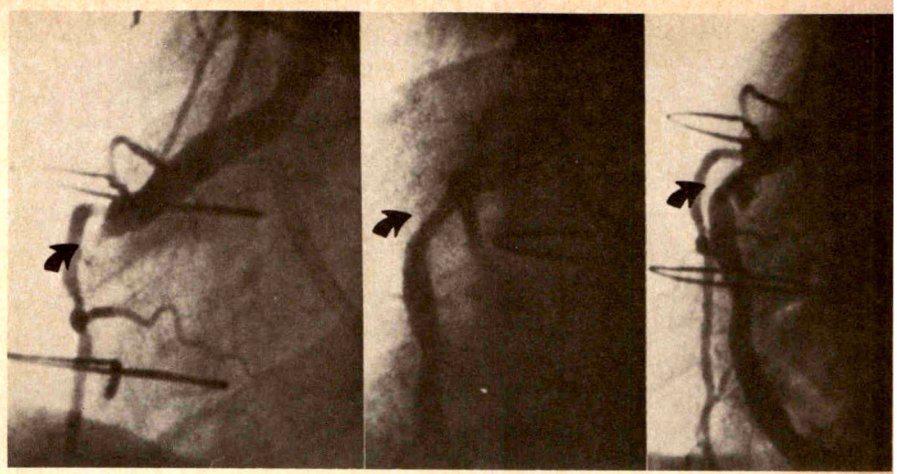

FIGURE 1. Case 1. Right coronary angiogram in left anterior oblique projection. **Left,** after intracoronary nitroglycerin but before streptokinase infusion and percutaneous transluminal coronary angioplasty (PTCA); **middle,** immediately after PTCA; **right,** 2 months after PTCA. **Arrows** indicate site of dilatation.

catheter was not advanced over a long distance within the coronary artery. In no patient did the balloon diameter appear to exceed the diameter of the native vessel viewed just proximal to the stenosis.

All patients received heparin, continuous infusions of nitroglycerin and low-molecular-weight dextran; 4 patients (Cases 2 to 5) received buccal nifedipine. However, 3 patients (Cases 1, 3, and 5) received intracoronary streptokinase during PTCA, with total doses of 15,000 to 122,000 IU. Administration of aspirin, dipyridamole, and nitrates was continued after PTCA.

Within hours of the dilatation procedure, 2 patients (Cases 1 and 5) had occlusion of the vessel undergoing PTCA. The other 3 had evidence of intimal disruption or abrupt reocclusion. There was no evidence at follow-up to suggest rupture of these aneurysms.

Results

Technical considerations: All patients had single-vessel PTCA performed by way of the femoral approach. In 2 patients (Cases 4 and 5) the guide catheter

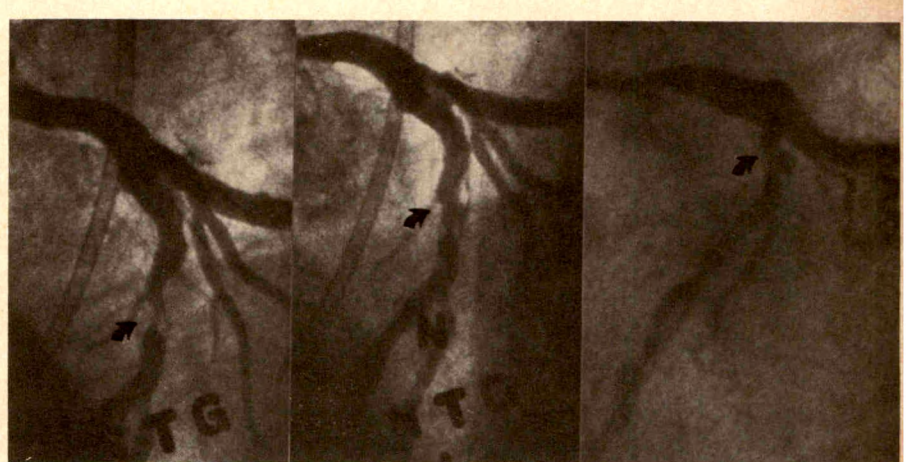

FIGURE 2. Case 2. Left coronary angiogram in left anterior oblique projection. **Left,** before percutaneous transluminal coronary angioplasty (PTCA); **middle,** immediately after PTCA; **right,** 4 months after PTCA. **Arrows** indicate site of dilatation.

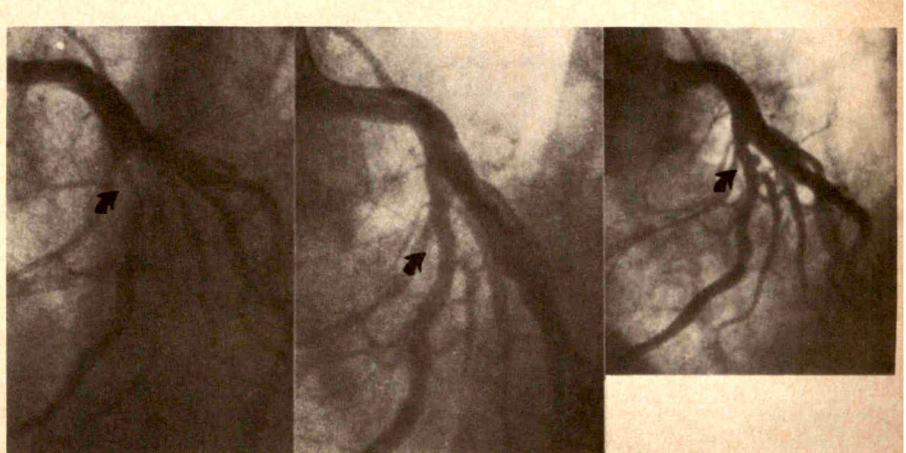

FIGURE 3. Case 3. Left coronary angiogram in left anterior oblique projection. **Left,** before percutaneous transluminal coronary angioplasty (PTCA); **middle,** immediately after PTCA; **right,** 4 months after PTCA. **Arrows** indicate site of dilatation.

as advanced deep into the left main coronary artery LAD to control the dilating catheter, but aneurysms veloped several centimeters beyond the guide cath-er. Commercially available dilating catheters, without novable guide wire, were used. Difficulty passing the lloon catheter across the stenosis occurred in only 1 tient (Case 4). All patients had multiple inflations (5 7 atmospheres) at the site of subsequent aneurysm rmation. There were no coronary artery perforations, ptured balloons, or emboli. Evidence of coronary asm was absent. In no patient was the dilatation a peat procedure.

Clinical course: At follow-up examination, 4 pa-nts had angina, prompting bypass surgery and drug erapy in 1 (Case 3). The other patient (Case 1) was ymptomatic at follow-up. The time to follow-up theterization, which first detected aneurysm forma-n, was 11 days to 4 months after PTCA. One patient ase 5) underwent cardiac catheterization 2 weeks ter PTCA and again at 3 months, but the aneurysm as present only at 3 months.

Discussion

These patients represent a very select group under-ing PTCA. These patients had complex clinical and atomic conditions and a high rate of complications. hether other clinical or technical differences were esent among these and other patients undergoing TCA without aneurysm formation is difficult to as-rtain. All these patients had an acute change related the coronary artery selected for PTCA, which is not aracteristic of most patients selected for this proce-re. Before PTCA, 2 patients had complete thrombotic clusions and another had a suspected nonocclusive rombotic defect, and intracoronary streptokinase was ven. Whether these circumstances contributed to neurysm formation is not known.

The complication rate with PTCA is 18.5%,[9] but to r knowledge formation of coronary arterial aneurysm the site of PTCA has not been reported. Follow-up theterizations are not done routinely in many centers, hich could account for lack of detection in some cases. he aneurysm would not have been detected in Patient if he had not undergone a second catheterization as art of follow-up, because he was asymptomatic.

The mechanism of improvement in coronary luminal ameter from PTCA is complex and includes plaque sruption, rupture of fissures, endothelial desquama-on and compression. Animal models show loss of en-othelium, plaque fracture with and without dissec-on-disruption of the internal elastic membrane, and atelet deposition.[3,4,5,10] In these animal studies there ere no acute occlusions but aneurysm formation oc-rred in 1 animal.[3] Human cadaver coronary arteries ith postmortem balloon angioplasty show medial and timal disruption.[2] Smooth muscle and medial con-ective tissue disruption occurs.[6] There are limitations trapolating these observations to live subjects. The ntributions of smooth muscle tone, motion, blood ow, and the healing process are unclear. The time urse of anatomic changes induced by PTCA is also known. Immediately after PTCA, a "hazy" con-ast-lumen interface often is seen at the site of angio-plasty.[1] This clears by the time of follow-up studies and perhaps represents intimal injury (edema, hemorrhage, and other factors) that heal over time. Small areas of linear radiolucency are also often seen immediately after dilatation. Whether this represents intimal disruption caused by separation of plaque fissures or intimal and medial dissection (that is, hematoma) remains unknown. Precisely what happens, over the long term, in areas where more extensive injury (such as dissection and occlusion) occurs is also unknown. The latter has particular relevance to our cases, because no evidence for aneurysm formation was present immediately after dilatation.

Whether initial local damage occurred coincident with exacerbation in symptoms that preceded or was secondary to PTCA cannot be determined. One could speculate, however, that PTCA-related damage caused medial weakening or disruption and the persistent hemodynamic stress dilated the weakened arterial wall. The fate of these PTCA-related aneurysms is unknown. Some have speculated that coronary aneurysms lead to embolization or thrombosis.[11–13] Rupture of a coronary aneurysm occurring in the natural course of coronary atherosclerosis is rare, if it occurs at all. PTCA-related aneurysms could have a different fate, however, if trauma or inflammation or both contributed to aneurysm development. Development of coronary aneurysm after PTCA emphasizes that our understanding of this new procedure is limited.

Acknowledgment: We thank Larry Kantor, MD, for permission to include Case 3, Tom Solloway for expert technical assistance, and Nancy Sajczuk for typing this manuscript.

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Results: No significant differences in endoscopic changes found between Slow-K and Micro-K at 96-mEq dosage.†

(Administered as four 8-mEq tablets or capsules, t.i.d.)

These data resulted from four different studies (involving 64 subjects) that used the maximum recommended daily dosage of 96 mEq before food ingestion and with concomitant administration of the maximum recommended dosage of the anticholinergic agent glycopyrrolate (6 mg).[1-4]

Maximum-dosage multistudy data

					Endoscopic findings‡			
N	Treatment	Daily dosage	Glycopyrrolate	Food	Ulcers	3	2	1
27	Slow-K	96 mEq	6 mg	No	1	1	6	12
37	Micro-K	96 mEq	6 mg	No	2	1	2	9

Results from similar studies supported by the A.H. Robins Company have shown a greater incidence of endoscopically observed GI irritation with Slow-K as compared to Micro-K when maximum doses of glycopyrrolate are administered.[5,6] These results, showing a significant difference between the products, are *inconsistent* with the data described herein, which do not show a significant difference.

High-dosage (48 mEq) multistudy data*

Results: No ulcers found with Slow-K or Micro-K. No significant differences in endoscopic changes found with Slow-K and Micro-K at 48-mEq dosage.

(Administered as two 8-mEq tablets or capsules, t.i.d.)

These data resulted from two different studies (involving 36 subjects) that used the high (48 mEq) dosage with food ingestion, and with and without the maximum recommended dosage of the anticholinergic agent glycopyrrolate. (Note: Glycopyrrolate was used in only one group of subjects on Slow-K.)[1,2] This 48-mEq dosage is higher than that normally used prophylactically.

High-dosage multistudy data

					Endoscopic findings‡			
N	Treatment	Daily dosage	Glycopyrrolate	Food	Ulcers	3	2	1
12	Slow-K	48 mEq	6 mg	Yes	0	0	2	6
12	Slow-K	48 mEq	None	Yes	0	0	0	4
12	Micro-K	48 mEq	None	Yes	0	0	1	5

*These studies were conducted by Drs. D. Patterson and G. Jeffries of the Hershey Medical Center, and by Dr. D. Earnest of the University of Arizona (Tucson).

†Also included in these multistudy data were an additional 70 subjects taking an 8-mEq sustained-release KCl capsule, a K^+ elixir, a sustained-release KCl tablet of higher mEq dosage than that currently available, or a placebo. The elixir and the placebo did not produce any endoscopic changes greater than two Grade 1 and five Grade 1 endoscopic findings, respectively. The higher dose sustained-release KCl tablets produced two ulcers, two Grade 2 and six Grade 1 endoscopic findings. The 8-mEq sustained-release capsule produced two Grade 2 and two Grade 1 findings. All Grade 1 endoscopic changes were considered clinically meaningless.

‡Grade 0 = no endoscopic findings
1 = hyperemia and/or edema (the medical consensus is that this category is clinically meaningless)
2 = few erosions
3 = numerous erosions (>3)
4 = ulceration
5 = multiple ulcerations

The anticholinergic agent glycopyrrolate was given to slow gastric emptying, thus ensuring maximum contact of the KCl supplements with the gastric mucosa. The impact, if any, of high-dose glycopyrrolate on the gastric mucosa is unknown.

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New epidemiologic study shows:

No difference between

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use and no K^+ therapy in the incidence of upper GI bleeding in a hospital setting.

SLOW-K: UNSURPASSED FOR SAFETY AMONG SLOW-RELEASE KCl CAPSULES OR TABLETS

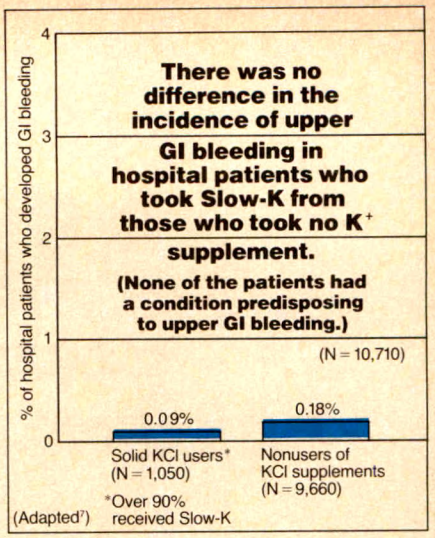
Experience of the Boston Collaborative Drug Surveillance Program[7]
As reported by Aselton and Jick in *Lancet*, January 22, 1983

Purpose of epidemiologic study:
To evaluate the relation between the use of wax-matrix KCl and the development of upper GI bleeding while in the hospital.

Patient population:
A total of 15,791 medical inpatients. Of those, 10,710 had no condition predisposing to upper GI bleeding. Of those, 1,050 received solid KCl* by mouth; 9,660 received no solid KCl.

Findings:
Of the 1,050 KCl users, 1 had GI bleeding (0.09%).
Of the 9,660 nonusers, 17 had GI bleeding (0.18%).

*Over 90% of this group received KCl in the form of Slow-K tablets.



Conclusion: "These findings argue against a positive association between wax matrix KCl use and upper gastrointestinal bleeding over a short period of time."[7]

These new data are consistent with the overwhelming evidence compiled in 8 years of use with Slow-K® potassium chloride slow-release tablets 8 mEq.

Analysis of 5.6 million U.S. patient-years' data: approximately one GI lesion per 100,000 patient-years—and this incidence rate has remained unchanged since Slow-K was introduced in 1975.[8]

*Method of determining incidence:
A: Includes all cases (most conservative method)
B: Excludes cases in which causality was unlikely and/or Slow-K was contraindicated
C: Excludes cases in which B was present *and* in which data were insufficient to assess causality (least conservative method)

Summary of lesion incidence rates per 100,000 patient-years

	Method* A	B	C
Esophagus	0.14	0.02	0.02
Stomach	0.27	0.14	0.11
Duodenum	0.12	0.05	0.05
Small bowel/large bowel; unknown location	0.82	0.43	0.27
Total	1.36	0.64	0.44

(Adapted[8])

Conclusion: Slow-K is a safe agent.

Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

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- Over 2 million additional patients in 1982 alone
- Over 51.8 million new and refill prescriptions
- 8 years' U.S. clinical experience
- 17 years' worldwide clinical experience
- 5.6 million U.S. patient-years of use
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(Data on file, CIBA Pharmaceutical Company.)

Do you have any questions concerning Slow-K? A member of the CIBA medical staff would be happy to answer them.

Please write to:
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Director of Professional Affairs
CIBA Pharmaceutical Company
556 Morris Avenue
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SLOW-K®
potassium chloride **slow-release tablets**

Brief Summary of Prescribing Information

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev. 1/83)

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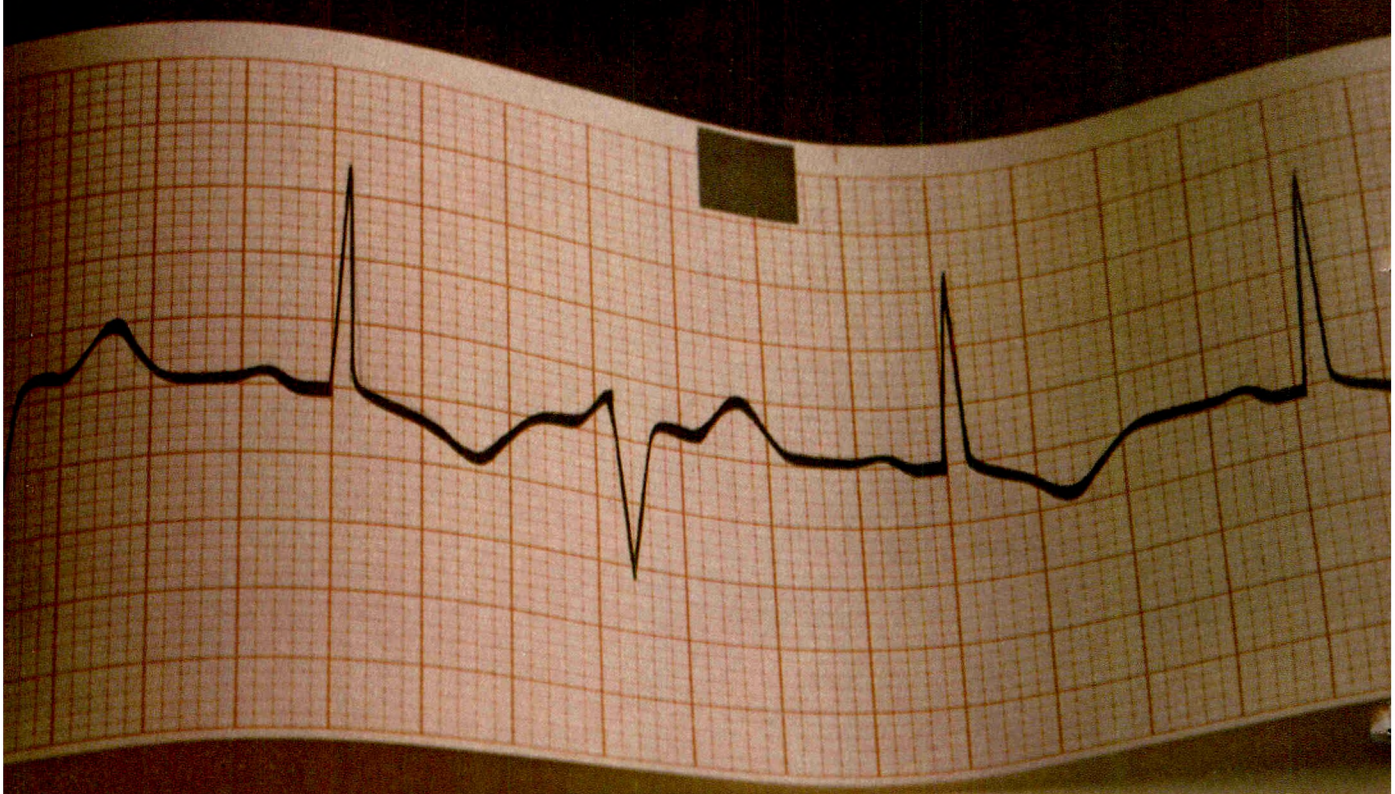

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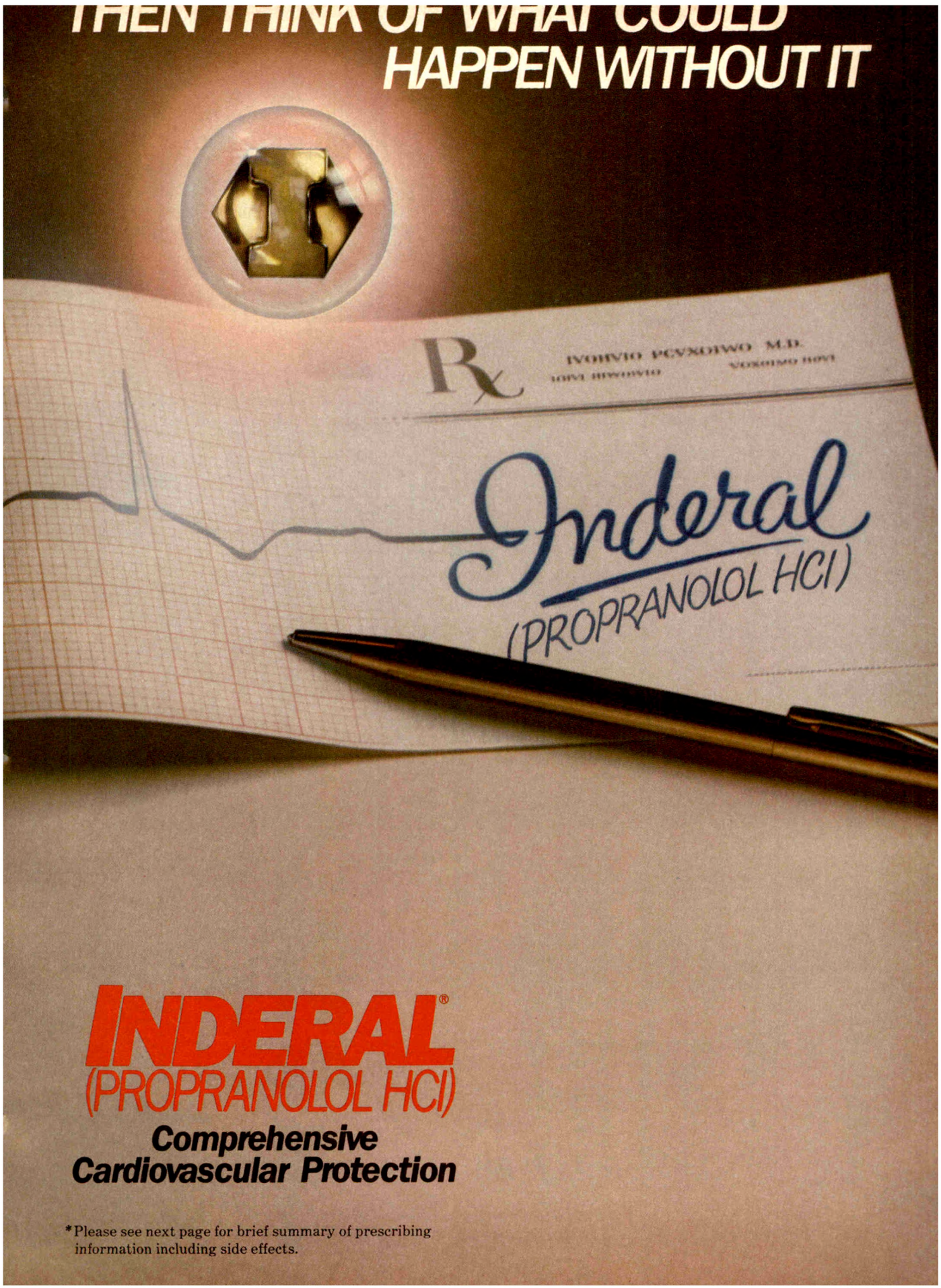

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IEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

pranolol hydrochloride is contraindicated in 1) bronchial asthma; 2) allergic rhinitis during pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic ock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart ure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with pranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO ibitors), and during the two week withdrawal period from such drugs.

WARNINGS

RDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory ction in congestive heart failure, and inhibition with beta blockade always carries the tential hazard of further depressing myocardial contractility and precipitating cardiac fail-. Propranolol acts selectively without abolishing the inotropic action of digitalis on the art muscle (i.e., that of supporting the strength of myocardial contractions). In patients eady receiving digitalis, the positive inotropic action of digitalis may be reduced by pro-anolol's negative inotropic effect. The effects of propranolol and digitalis are additive in pressing AV conduction.

N PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the ocardium over a period of time can, in some cases, lead to cardiac failure. In rare tances, this has been observed during propranolol therapy. Therefore, at the first sign or mptom of impending cardiac failure, patients should be fully digitalized and/or given a iuretic, and the response observed closely: a) if cardiac failure continues, despite adequate gitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if hyarrhythmia is being controlled, patients should be maintained on combined therapy and patient closely followed until threat of cardiac failure is over.

N PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against nterruption or cessation of therapy without the physician's advice. If propranolol therapy s interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent o follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

N PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use ve not been adequately appraised. Special consideration should be given to propranolol's tential for aggravating congestive heart failure. Propranolol may mask the clinical signs of veloping or continuing hyperthyroidism or complications and give a false impression of provement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbaon of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withawing propranolol slowly. Propranolol does not distort thyroid function tests.

N PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been orted in which, after propranolol, the tachycardia was replaced by a severe bradycardia quiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

N PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the art to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and ysiologic effects are gone according to available evidence. However, in case of emergency rgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, ch patients may be subject to protracted severe hypotension. Difficulty in restarting and intaining the heart beat has also been reported.

N PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine-blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

TABLETS

—Each hexagonal-shaped, orange, scored tablet is embossed with an "I" and imprinted with "INDERAL 10," contains **10 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0421-81) and 1,000 (NDC 0046-0421-91). Also in unit dose package of 100 (NDC 0046-0421-99).

—Each hexagonal-shaped, blue, scored tablet is embossed with an "I" and imprinted with "INDERAL 20," contains **20 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0422-81) and 1,000 (NDC 0046-0422-91). Also in unit dose package of 100 (NDC 0046-0422-99).

—Each hexagonal-shaped, green, scored tablet is embossed with an "I" and imprinted with "INDERAL 40," contains **40 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0424-81) and 1,000 (NDC 0046-0424-91). Also in unit dose package of 100 (NDC 0046-0424-99).

—Each hexagonal-shaped, pink, scored tablet is embossed with an "I" and imprinted with "INDERAL 60," contains **60 mg** propranolol hydrochloride, in bottles of 100 (NDC 0046-0426-81) and 1,000 (NDC 0046-0426-91). Also in unit dose package of 100 (NDC 0046-0426-99).

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The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Store at room temperature (approximately 25° C).

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8226/483

The Automatic Implantable Defibrillator: Local Ventricular Bipolar Sensing to Detect Ventricular Tachycardia and Fibrillation

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The first-generation automatic implantable defibrillator implanted in man sensed arrhythmias by monitoring a transcardiac electrocardiographic signal. This sensing system reliably detected ventricular fibrillation and sinusoidal ventricular tachycardia but failed to sense all nonsinusoidal ventricular tachycardias. To solve this problem, a new ventricular tachycardia detection scheme was developed using a local ventricular bipolar electrogram and electronic circuits using rate averaging and automatic gain control to permit sensing of electrograms down to 0.1 mV. This detection scheme was tested during electrophysiologic studies in 11 patients with ventricular tachycardia and fibrillation. All 22 episodes of induced ventricular tachycardia with a rate above the selected cutoff were detected after an average of 5.1 ± 1.8 seconds. No episodes below the rate cutoff were detected. The bipolar circuits also reliably detected ventricular fibrillation. Arrhythmia detection and signal quality in 9 patients receiving automatic defibrillators using the new bipolar rate detection circuit were compared with the findings in 5 patients previously receiving units that sensed arrhythmias using the transcardiac electrocardiographic signal. Compared with the transcardiac monitoring units the newer bipolar units had shorter and more uniform sense times (5.5 ± 1.4 versus 12.2 ± 7.1 seconds). It is concluded that malignant ventricular tachyarrhythmias can be sensed accurately using bipolar rate detection and that this system has numerous advantages over the previously used transcardiac electrocardiographic signal.

Observations made in coronary care units in patients with acute myocardial infarction and the rhythms identified in out-of-hospital cardiac arrest victims at the time of arrival of paramedic units suggested that ventricular fibrillation (VF) was responsible for most of these deaths. These observations led Mirowski et al[1] to propose the concept of an automatic implantable defibrillator. This group demonstrated that defibrillation using catheters and other electrode configurations was possible in both animals[2] and man[3] using energy levels considerably below those required for transthoracic cardioversion. Early versions of the automatic defibrillator were designed to distinguish between VF or sinusoidal ventricular tachycardia (VT)[4] and supraventricular or nonsinusoidal VT. This was accomplished using an electrocardiographic signal derived from an extrapericardial patch sutured to the apex of the heart and a superior vena caval spring electrode (the same leads used for delivering the defibrillation shock). A probability-density function describing the relative durations of isoelectric and nonisoelectric activity of the signal was determined electronically to identify VF which produces a predominantly nonisoelectric signal. In the late 1970s, arrhythmia induction using programmed electrical stimulation in survivors of out-of-hospital cardiac arrest suggested that many terminal arrhythmias begin as a rapid nonsinusoidal VT.[5] These observations have been confirmed in many patients fortuitously wearing ambulatory electrocardiographic recorders at the time of sudden death.[6] Shortly after the first human implant of the automatic defibrillator, this

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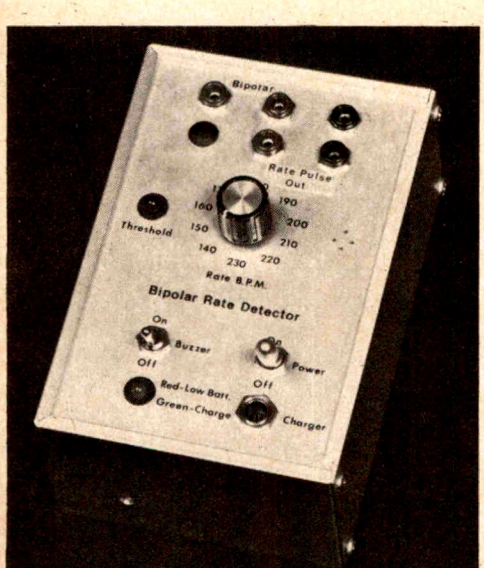
be used in some patients with nonsinusoidal VT. However, the transcardiac electrocardiographic signal ecorded from the patch and spring has a number of mitations for rate counting, including double counting f heart rate in some patients due to large amplitude P aves[7] as well as postshock ST-T abnormalities which ould cause difficulties in postshock rhythm identifiation. Furthermore, some patients with VT at rates xceeding the rate setting of the defibrillator did not ave the arrhythmia sensed because of failure of the VT satisfy the probability-density function. A local entricular bipolar electrogram was developed to proide a signal more suitable for rate detection. The lectronic sensing was specifically designed to sense the w-amplitude fragmented electrograms that occur uring VF but not to sense noise, T waves, and P waves uring sinus rhythm. The sensing system can deal with gnals of varying morphologic characteristics and mplitude, such as those occurring during episodes of olymorphic VT.

This report describes our evaluation of this sensing heme in a group of patients being studied in the ectrophysiology laboratory. It also details our clinical xperience in 9 patients who received an implanted efibrillator using local ventricular bipolar sensing and ompares the sensing to that observed in our first 5 atients who received automatic implantable defibrilators without local ventricular bipolar sensing.

Methods

Preliminary testing: Ten patients aged 53 to 72 years ndergoing 16 electrophysiologic studies for antiarrhythmic rug selection were the subjects of this part of the study. The agnosis was coronary disease in 9 and primary myocardial sease in 1.

A standard quadripolar USCI® 6Fr temporary pacing theter with 1-cm interelectrode distances was positioned the right ventricular apex. The proximal pair of electrodes ovided the bipolar input for a battery-operated bread-board



model (Fig. 1) of the new rate detection circuits. These circuits perform rate averaging, which requires longer runs of VT to satisfy the sensing criteria when the preceding sinus rhythm is slow than when it is rapid, and requires more time for sensing when there are occasional nonsensed QRS complexes. The circuit uses automatic gain control, which permits reliable detection of signals as small as approximately 0.1 mV. This bread-board model contained only the sensing circuit and did not deliver a cardioverting or defibrillating shock. With each ventricular electrogram the circuits provided an audible beep and a 180-ms square-wave output. The heart rate criterion for tachycardia detection could be preselected from 140 to 230 beats/min in increments of 10 beats/min. Once the rate of a tachycardia was consistently above the preselected rate, it was "sensed," the beep tone became continuous, and the gain of the square-wave output was manually decreased.

Electrophysiologic study was performed in the usual manner, with ventricular tachyarrhythmias induced using 1 to 3 ventricular extrastimuli in either sinus rhythm or ventricular drive. Multiple surface leads, 1 or more intracardiac leads, femoral aortic pressure, and the square wave from the bread-board rate detection circuit were displayed on a strip chart recorder. For each episode of induced VT the time and number of QRS complexes from onset of tachycardia to sensing by the rate detection circuit was recorded.

Implanted defibrillators: Rate detection circuits similar to those tested in the electrophysiology laboratory were incorporated into the automatic implantable defibrillator. This new model is the AID-B® and has been implanted in 9 patients at Stanford Medical Center. In all patients the clinical indication for implantation was drug-resistant recurrent VT or VF. All patients underwent left lateral thoracotomy for implantation of the standard apical patch electrode and a pair of Medtronic 6917A-53T screw-in electrodes for the local ventricular bipolar sensing signal. The screw-in leads were positioned in the area of healthiest appearing ventricular myocardium, generally near the anterobasal portion of the left ventricle. The superior vena caval spring electrode was placed through the left subclavian vein using the Seldinger technique. At the time of implant the unfiltered signal was recorded from local ventricular bipolar leads as well as from spring-patch transcardiac leads. VT was induced for measurement of defibrillation/cardioversion thresholds as well as for testing the AID-B unit after the generator was connected to the leads. For episodes of VT and VF induced with the AID-B generator connected to the leads, the time from onset of arrhythmia to sensing was determined. For these 9 patients the signal amplitude and quality from the local ventricular bipolar pair was compared with that of the transcardiac electrocardiographic signal. In addition, sense times for the AID-B unit with local bipolar sensing was compared with results obtained in our first 5 implants of AID® units, which used the transcardiac spring-patch system for rate detection rather than local bipolar rate sensing. All statistical comparisons were made using a 2-tailed t test for either paired or unpaired data when appropriate.

Results

Testing during electrophysiologic study: Forty-four episodes of VT were induced in the 10 patients. The rate criterion was selected to be slightly below the rate of the patient's previously documented VT and was 140 beats/min for 12 episodes, 150 beats/min for 14 episodes, 160 beats/min for 17 episodes, and 180 beats/min for 1 episode. A typical episode of VT induction and sensing by the rate detection circuit is shown in Figure

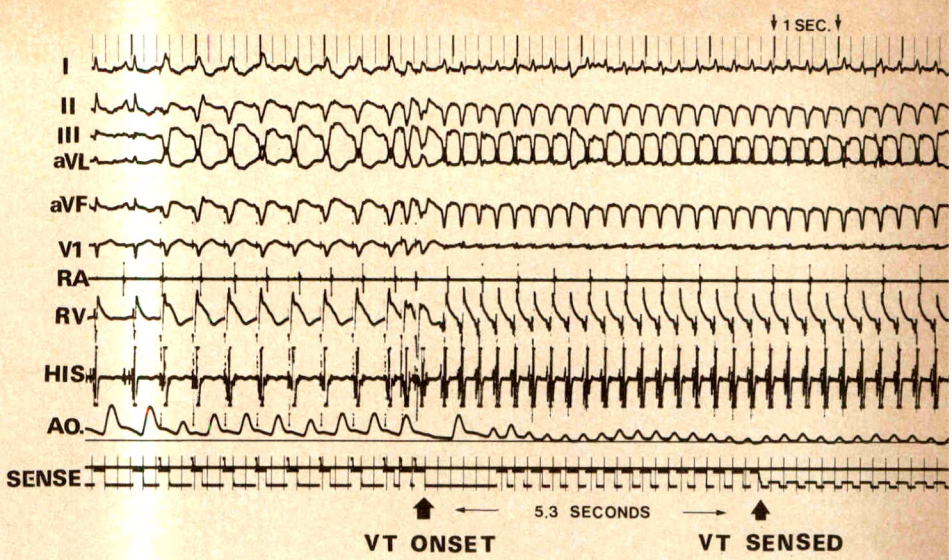


FIGURE 2. A typical episode of ventricular tachycardia (VT) induction and sensing by the rate detection circuit. Shown are surface leads I, II, III, aVL, and V_1 as well as a right atrial (RA) bipolar electrogram, a right ventricular (RV) unfiltered bipolar electrogram, electrograms recorded from the His position and systemic arterial pressure (AO). The line labeled SENSE shows the square-wave output of the rate detection circuit. VT is initiated by a pair of ventricular extrastimuli given in ventricular drive and is labeled VT ONSET. Then, 5.3 seconds later, the beeping tone of the bread-board circuits are continuous and the gain of the square-wave output decreases. This is the time at which the device sensed VT. Had a defibrillator actually been implanted, this VT sensing would have initiated a charging cycle and a shock would have been delivered approximately 7 seconds later.

implanted in these patients, sensing by the rate detection circuit would have initiated charging of the capacitors which store the defibrillation/cardioversion shock. The delay from time of arrhythmia sensing until delivery of the converting shock is 7 to 10 seconds.

Figure 3 shows the outcome in the 44 episodes of induced VT. Eleven episodes spontaneously terminated after 8 to 19 QRS complexes. Three of these episodes were sensed by the device after 11, 12, and 15 beats, or 3.5, 4, and 5 seconds, respectively. These 3 episodes would have spontaneously terminated before delivery of a converting shock (7 to 10 seconds later) had a defibrillator been in place, and an R-wave synchronous shock would have been delivered during sinus rhythm. Thirty-three episodes of VT were sustained and did not terminate until rapid pacing or external transthoracic cardioversion was performed. The average rate of the induced tachycardia and the number of QRS complexes and time from onset until sensing is summarized in Table I. All 22 episodes of VT with rates above the preselected setting on the bread-board circuit were sensed after an average of 5.1 ± 1.8 seconds. Two episodes of induced VT with rates virtually identical to the preselected rate were sensed after 19 and 21.5 seconds. Nine episodes of induced VT were below the cutoff rate selected and none were sensed as a rhythm to be shocked despite persistence for several minutes or longer in most patients. Neither the time elapsed from onset of VT until sensing nor the number of QRS complexes elapsed before sensing was clearly a function of the underlying rate of the VT (Fig. 4 and 5).

In addition to the 44 episodes of VT induced during ventricular drive or sinus rhythm, 10 VTs of different morphologic characteristics and rate and 6 episodes of VF were induced during attempts at tachycardia termination by pacing. All 16 episodes were sensed by the rate detection circuit.

Clinical experience: Fourteen patients have had automatic defibrillators implanted at Stanford Medical Center. The first 5 patients received AID devices using arrhythmia detection based on the probability-density function and heart rate derived from the transcardiac spring-patch electrode pair. The last 9 patients received AID-B devices using a local ventricular bipolar rate detection circuit similar to the one tested in the electrophysiology laboratory. The initial 5 patients had 16 episodes of VT or VF induced at implant or predischarge electrophysiologic study. Two episodes were not sensed because of failure to satisfy the probability density function. The sensing time for the 14 other episodes was 12.2 ± 7.1 seconds (range 5.6 to 27.6). The 9 patients who received the AID-B devices with the new local ventricular bipolar sensing circuit had a total of 29 episodes of VT or VF induced at the time of implant or

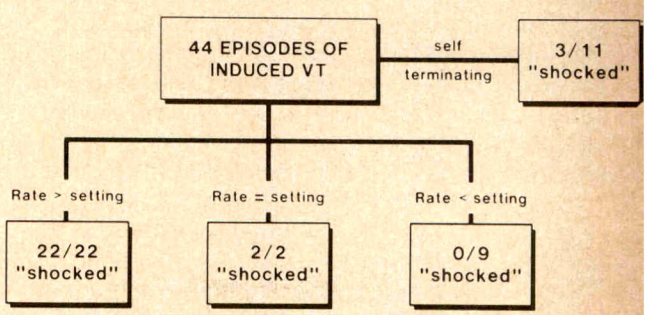
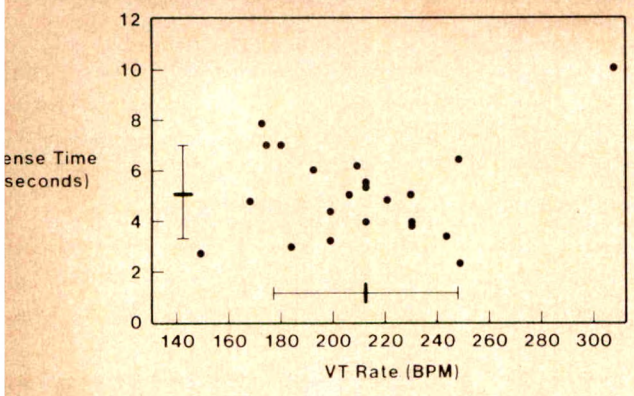


FIGURE 3. Outcome in 44 episodes of induced ventricular tachycardia (VT).

TABLE I Summary of Sensing Data for 44 Episodes of Ventricular Tachycardia (VT)

	Rate >Setting	Rate = Setting	Rate <Setting
Number of episodes	22	2	9
VT rate	212 ± 36	140,150	130 ± 15.6
QRS's to sensing	18 ± 8.0	50,51	—
Time to sensing	5.1 ± 1.8	21.5,19	



GURE 4. Time (in seconds) from the onset of ventricular tachycardia T) until it was sensed by the rate detection circuits as a function of e ventricular tachycardia rate.

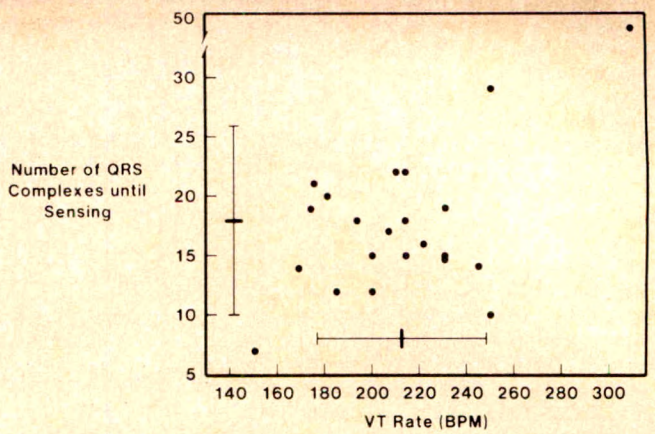


FIGURE 5. The number of QRS complexes from the onset of ventricular tachycardia (VT) until sensing by the rate detection circuits as a function of the ventricular tachycardia rate.

uring postoperative electrophysiologic study. All 29 pisodes were appropriately sensed with an average ensing time of 5.5 ± 1.4 seconds (range 3.4 to 7.8). The atients receiving the AID-B automatic implantable efibrillator with local bipolar sensing had more uni- orm and shorter ($p = 0.01$) sensing times than did pa- ents receiving AID units without this type of ensing.

For patients receiving the AID-B defibrillators, it was ossible to compare the signal amplitude and quality f the local bipolar electrogram to that of the simulta- eously recorded transcardiac spring-patch signal uring both sinus rhythm and induced ventricular ar- ıythmias. In sinus rhythm the average amplitude of ıe unfiltered local bipolar electrogram was consider- bly greater than that of the spring-patch (10.4 ± 7.15 ıV versus 4.1 ± 3.1 mV). During 25 episodes of induced T the average local ventricular bipolar signal ampli- ıde was 9.9 ± 10.4 mV and the amplitude across the ring-patch lead was 5.2 ± 3.0 mV. Six of the 9 patients ad considerably larger electrograms during VT in the ipolar lead compared with the spring-patch lead, in 1 atient signal amplitudes were approximately identical nd in 2 patients electrogram amplitude was greater in ıe spring-patch lead. There was considerable post- ıock signal distortion in the spring-patch electrocar- iographic signal due to S-T segment changes. Post- ıock signal distortion was minimal in the local bipolar ntricular electrogram.

The opportunity to directly compare the sensing time f the old AID system to the sensing time of the new ipolar rate detection system occurred during an elec- ophysiologic study in 1 patient who had an automatic nplantable defibrillator using transcardiac rate de- ction rather than the new local ventricular bipolar rcuit. The new rate detection circuit sensed the ıythm approximately 3 seconds earlier than did the nplanted device (Fig. 6).

In 13 of the 14 patients, all sensed episodes of VT or F were terminated with a single shock from the auto- atic implanted defibrillator. In 1 patient the energy the shocks delivered from the spring-patch electrode stem was insufficient to consistently terminate VF. In this patient, the use of a pair of patch leads for delivering the shocks resulted in termination of 7 consecutive episodes of induced VF, each with a single shock. The average energy delivered from the devices implanted in these 14 patients was 24.9 ± 2.4 joules (range 23 to 30).

Discussion

Reliable sensing of VT and VF is not a simple task. Sensing circuits must detect low-amplitude fragmented electrograms that may occur during VF, but must not sense noise during sinus rhythm. There must be short refractory periods to detect rapid ventricular rates even though these short refractory periods increase the likelihood of inappropriate sensing of T waves and noise. These circuits must also be able to detect arrhythmias associated with a rapidly changing electrocardiographic morphology and amplitude such as occurs during polymorphic VT or torsades de pointes.

Even more difficult than detecting VT and VF is distinguishing between supraventricular tachycardia (SVT) with aberration and VT. On the basis of surface electrocardiograms, this distinction is often difficult and sometimes impossible. Fully morphology-dependent arrhythmia detection systems such as the probability-density function will not distinguish all SVTs from VTs, because some patients with preexisting bundle branch block will have wider and more abnormal QRS complexes during SVT than during episodes of VT. Furthermore, many patients with recurrent sustained VT have markedly different morphologic characteristics from 1 episode of tachycardia to the next. The availability of atrial and ventricular electrograms for arrhythmia definition cannot reliably distinguish these 2 rhythms, because virtually any relation between atrial and ventricular activation may occur. Typical examples include complete atrioventricular dissociation, 1 to 1 relations between atria and ventricles with atrial electrograms simultaneous with, after, or preceding each ventricular electrogram and a spectrum of anterograde and retrograde block. Furthermore, atrioventricular

relations may differ in the same patient from 1 episode to the next depending on autonomic tone, rate of tachycardia, and presence or absence of antiarrhythmic therapy. Detection schemes relying on monitoring of arterial pressure to define rhythms that should be shocked are not fully reliable either, because many patients with poor left ventricular function will decompensate as much from SVT as from VT, whereas patients with reasonably good ventricular function may tolerate rapid VTs. Currently, we cannot envision a practical system for reliably distinguishing all SVT, especially those with aberrant conduction from VT.

The rate detection circuits evaluated in the present study never failed to sense an episode of VT whose rate exceeded the preselected rate cutoff. The rate averaging and automatic gain control features also provide reliable detection of polymorphic VT and VF. The availability of these rate detection circuits markedly expands the number of patients for whom an automatic implanted defibrillator may provide life-saving therapy from a relatively small group with sinusoidal VT or VF to the much larger group with recurrent sustained VT. In over 50 hours of evaluation in the electrophysiology laboratory and 40 patient-months of follow-up, this system has not been documented to have inappropriately sensed T waves or noise.

Detection of ventricular tachyarrhythmias based on rate alone is not a perfect method. Any sinus or other tachycardia will satisfy the detection scheme and clinically inappropriate shocks may be delivered. Furthermore, selection of an appropriate rate for each patient can be difficult. For many patients there may be overlap in the maximum sinus rates achieved during activity or emotional stress and the rates of ventricular tachyarrhythmias, especially in patients receiving antiarrhythmic therapy. Furthermore, the rate of VT may vary from 1 episode to the next or when antiarrhythmic drug therapy changes. Nonetheless, it remains possible to select for most patients a rate cutoff criterion which is not frequently achieved by their sinus mecha-

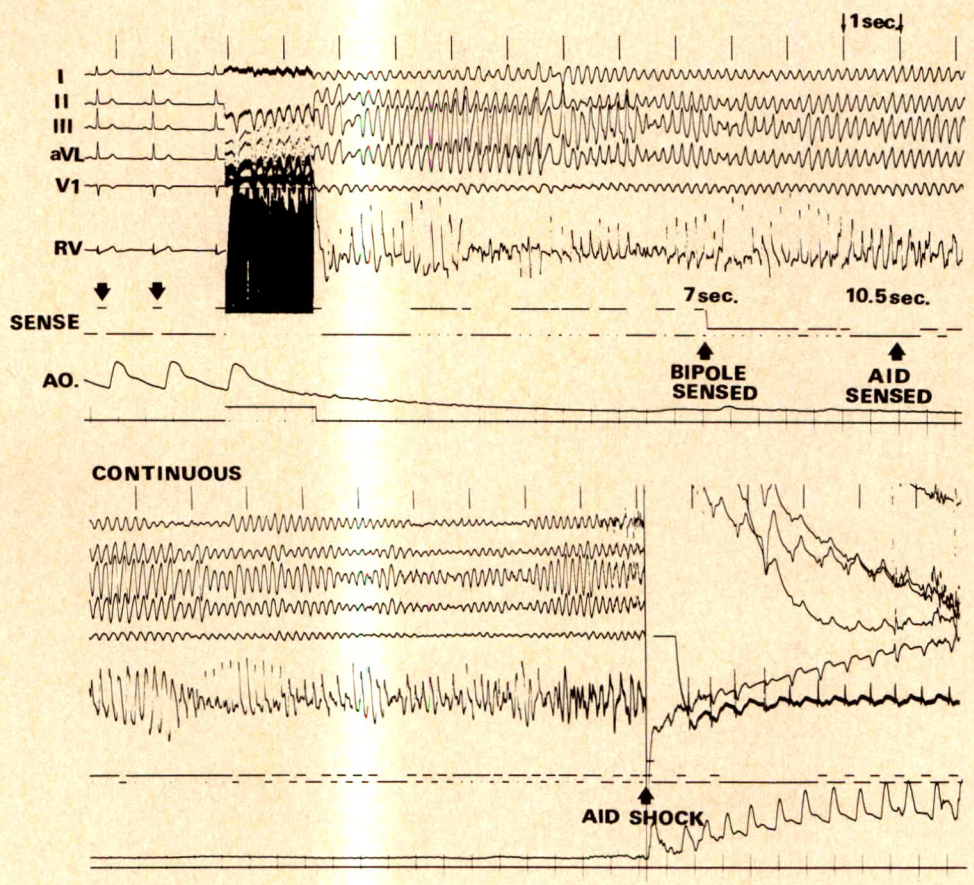


FIGURE 6. Comparison of the sensing time of the new bipolar rate detection circuits and the old arrhythmia detection circuits using the spring-patch electrode. These recordings were made at the time of electrophysiologic study in a patient with a previously implanted automatic defibrillator which used spring-patch sensing. At the time of electrophysiologic study, a right ventricular bipolar signal provided input for the bread-board circuit, so that the sensing time of the new bipolar circuits could be directly compared with that of the previous automatic implanted defibrillator (AID). Shown in the **upper** and **lower panels** is a continuous electrocardiographic strip showing surface leads I, II, III, aVL, and V_1 as well as a right ventricular electrogram (RV), the square-wave sensing output of the bread-board circuit (SENSE), and the systemic arterial pressure (AO). During sinus rhythm ventricular fibrillation is induced with a brief burst of pacing at cycle length 10. Most of the right ventricular electrograms during ventricular fibrillation are sensed by the bipolar circuit as indicated by the square-wave output. After 7 seconds of ventricular fibrillation the bipolar circuits sensed the arrhythmia, the beeping tone became continuous, and the gain of the square-wave output was decreased. It was not until 3.5 seconds later (10.5 seconds after the onset of ventricular fibrillation) that the AID using spring-patch sensing sensed this arrhythmia. The AID automatically began charging and delivered a shock approximately 11 seconds later, which terminated the ventricular fibrillation.

ism and which is below that of the VT one desires to erminate. The rate detection circuits may also be used n conjunction with a morphology-dependent criteria, uch as the probability-density function, to minimize he possibility of delivery of shocks during sinus or other arrow-QRS SVT. However, the addition of a morphology-dependent criterion is done at the expense of ncreasing the likelihood that some VTs will not be ecognized by the system.

Selection of the appropriate rate cutoff and incorporation of a sensitivity setting for probability density unction must be made on an individual patient basis. The availability of external programmability in the near uture will enhance the ability to customize the implanted defibrillator to individual patient's needs. To late the delivery of synchronized shocks during sinus hythm has not been associated with significant morality or morbidity except for discomfort. It has been our philosophy to select devices that are unlikely to fail to letect a serious ventricular tachyarrhythmia but that may occasionally deliver a shock for a sinus or other SVT. Further refinements in programmability of devices and detection schemes should improve the ratio of clinically appropriate to inappropriate shocks.

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Effects of Oral Diltiazem in Paroxysmal Supraventricular Tachycardia

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Electrophysiologic studies were performed before and 2 hours after the oral administration of 270 mg of diltiazem in 3 divided doses at 8-hour intervals in 36 patients with paroxysmal supraventricular tachycardia (SVT). Before diltiazem, all 36 patients had induction of sustained SVT: 24 with atrioventricular (AV) reentrance incorporating an accessory pathway (Group 1) and 12 with AV nodal reentrance (Group 2). After diltiazem, 20 patients in Group 1 lost the ability to induce or sustain SVT because of increased anterograde normal pathway refractoriness in 19 patients and increased retrograde accessory pathway refractoriness in 1. Eight patients in Group 2 could no longer induce or sustain SVT because of increased anterograde slow pathway refractoriness in 2 patients and increased retrograde fast pathway refractoriness in 6. Diltiazem concentration in the blood, measured in 29 patients, was 156 ± 75 ng/ml (mean ± standard deviation). Fifteen patients, 2 with and 13 without induction of sustained SVT after diltiazem, were discharged on the same dosage of diltiazem and followed up 5 ± 3 months. The former 2 patients had attacks of sustained SVT, whereas the latter 13 have been free of sustained SVT. In conclusion, oral diltiazem prevents induction and sustenance of paroxysmal SVT in most patients and may be used as an alternative agent for the prophylaxis of SVT.

Diltiazem is 1 of the more promising calcium antagonists proved effective in the management of angina pectoris. Similar to verapamil, diltiazem is electrophysiologically potent, capable of depressing atrioventricular (AV) nodal conduction.[1–4] Limited clinical data have shown that intravenous diltiazem terminates paroxysmal supraventricular tachycardia (SVT) and slows the ventricular rate during atrial fibrillation.[5–7] However, systematic studies on the electrophysiologic effects of diltiazem in patients with paroxysmal SVT are lacking. In this study we evaluated the effects of oral diltiazem on the induction and sustenance of paroxysmal SVT in a large group of patients.

Methods

Patients: The study population consisted of 36 patients, 21 male and 15 female, aged 17 to 69 years (mean ± standard deviation 37 ± 15). All study patients had electrocardiographic documentation of recurrent SVT, which could be electrophysiologically induced on the day of the control study. Of the 36 patients, 33 had no demonstrable organic heart disease, and 3 had a history of systemic hypertension.

Electrophysiologic studies: Each patient gave written informed consent. Electrophysiologic studies were performed in the supine, postabsorptive, and nonsedated state. Cardioactive drugs were discontinued at least 5 half-lives before the study. A #7 quadripolar electrocatheter was introduced percutaneously into the right femoral vein and positioned across the tricuspid valve; the proximal 2 electrodes were used for His bundle recording, whereas the distal 2 electrodes were used for right ventricular pacing. A #7 hexapolar electrodecatheter was introduced through cutdown to the right antecubital vein and advanced to the coronary sinus. In this position, the proximal 4 electrodes were located against the lateral wall of the high right atrium near the junction of the superior vena cava. The distal 2 electrodes were used to record the left atrial electrogram from the coronary sinus, the middle 2 to record the high right atrial electrogram, and the proximal 2 for right atrial pacing. Multiple surface and intracardiac electrograms were simultaneously displayed and recorded on a multichannel oscilloscopic photographic recorder (Electronics for Medicine VR-16, White Plains, New York) at paper speeds of 100, 150, and 250 mm/s, and at a filter setting between 30 and 500 Hz. Stimuli 2 ms in duration and approximately twice the diastolic threshold were delivered by a pro-

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grammable digital stimulator (DTU PC 100, Bloom and Associates, Narberth, Pennsylvania).

The study protocol included (1) incremental atrial pacing to the atrial paced cycle length that induced AV block, (2) atrial extrastimulus testing (A_1 A_2 testing) at sinus and a driven cycle length of 600 or 500 ms, and double extrastimulus testing (A_1 A_2 A_3 testing) in those patients in whom A_1 A_2 failed to induce either echo beats or SVT, (3) incremental ventricular pacing to the paced cycle length that induced ventriculoatrial (VA) block, (4) ventricular extrastimulus testing (V_1 V_2 testing) at driven cycle lengths of 600 or 500 or both, (5) mapping of the atrial activation sequence during induced SVT, and (6) delivery of a ventricular extrastimulus during induced SVT. At the completion of the control study, the tip of the hexapolar catheter was repositioned at the right ventricular apex, and the proximal 4 electrodes were maintained in the initial atrial positions. The hexapolar catheter was then secured for subsequent electrophysiologic studies. The quadripolar electrocatheter was removed. The patient was then given oral diltiazem (release-controlled tablet, Tanabe Seiyaku Co, LTD, Osaka, Japan), 90 mg every 8 hours, and the electrophysiologic studies were repeated 2 hours after the third dose of diltiazem. In 29 patients blood samples were taken at the time of the electrophysiologic studies to measure plasma diltiazem concentration using thin-layer chromatography[8,9] (measured by Tanabe Seiyaku Co, LTD, Osaka, Japan).

Electrophysiologic definitions: Anterograde properties were evaluated by noting the longest atrial paced cycle length that induced 2° AV block and by measuring the effective refractory period of the AV conducting system. Retrograde properties were evaluated by noting the longest ventricular paced cycle length that induced VA block and by measuring the effective refractory period of the VA conduction system. For comparison, pre- and postdiltiazem values of anterograde properties were measured from the high right atrial electrogram at identical driven cycle lengths. Conduction intervals and refractory periods were defined and measured as previously described.[10,11] The incorporation of an accessory pathway for retrograde conduction during induced SVT was suggested by (1) an abnormal atrial activation sequence during induced SVT, (2) an increment in VA conduction time with the development of bundle branch block ipsilateral to the accessory pathway during induced tachycardia, and (3) the ability to capture the atrium by a critically timed ventricular extrastimulus given during SVT when the His bundle was noted to be refractory.[10–16] The diagnosis of AV nodal reentrant tachycardia was made using previously described criteria, and the possibility of AV and atrial reentrant tachycardia was excluded.[11–17]

Sustained SVT is defined as an episode of induced SVT >2 minutes in duration which requires termination with electrical stimulation. Nonsustained SVT after diltiazem is defined as all episodes of induced SVT that terminate spontaneously within 10 seconds. Anterograde weak-link of the reentrant circuit refers to termination of either echoes or SVT that occurs with an atrial response that is not followed by a ventricular response. Retrograde weak-link of the reentrant circuit refers either to termination of echoes or SVT that occurs with a ventricular response that is not followed by an atrial response or to the achievement of an HRA-V interval that is longer than the observed control critical AV interval without the induction of AV or AV nodal reentrant echoes.

Data analysis and follow-up: Data were expressed as mean ± standard deviation and were analyzed with the paired Student t test. Fifteen patients were discharged on oral diltiazem, 90 mg every 8 hours, and were followed up in the clinic for 5 ± 3 months.

Results

Of the 36 patients, 24 had AV reentrant tachycardia incorporating an accessory pathway conducting retrogradely (Group 1) and 12 of the 36 patients had AV nodal reentrant tachycardia using a slow pathway for anterograde and a fast pathway for retrograde conduction (Group 2). Ten of the former 24 patients had ventricular preexcitation, whereas 14 had a concealed accessory pathway.

Effects on AV reentrant tachycardia (Table I, Cases 1 to 24; Fig. 1 and 2): In all 24 patients, sustained SVT could be induced before diltiazem. After diltiazem, sustained SVT could be induced in only 4 patients (Cases 1 to 4), nonsustained SVT occurred in 3 patients (Cases 5 to 7) (Fig. 2), a single AV reentrant atrial echo occurred in 12 patients (Cases 8 to 19), (Fig. 1), and neither SVT nor an echo could be induced in 5 patients (Cases 20 to 24). Of the 15 patients in whom either nonsustained SVT or a single AV reentrant atrial echo could be induced after diltiazem, the weak link occurred in the anterograde direction in 14 patients (Fig. 1D) and in the retrograde direction in 1 patient (Case 7) (Fig. 2D). In the 5 patients in whom neither SVT nor echo could be induced after diltiazem, the factor limiting induction was either failure to achieve a critical AV interval (Case 20) or failure of normal pathway conduction due to a longer refractoriness of the normal pathway than of the accessory pathway (Cases 21 to 24).

The cycle length of the SVT could be compared before and after diltiazem only in 7 patients (Cases 1 to 7) in whom SVT could be induced after diltiazem. In these 7 patients, the cycle length of the SVT was 349 ± 61 ms (range 290 to 450) before and 399 ± 51 ms (range 310 to 445) after diltiazem (difference not significant [NS]). The cycle length of the SVT lengthened in 6 patients and shortened in 1. The changes in cycle length of the SVT reflected changes in the AV interval, because the VA interval remained unchanged after diltiazem.

The longest atrial paced cycle length that induced 2° AV block could be compared in 20 patients (Cases 1 to 5, 8, 10 to 23) and increased from 301 ± 67 ms (range <240 to 400) before to 397 ± 67 ms (range ≥260 to 500) after diltiazem ($p < 0.001$) (Fig. 1A and 1C). Measurement of the anterograde effective refractory period was frequently impossible after diltiazem because of the occurrence of echoes or second-degree (2°) AV block, or both, at the basic driven cycle length (Fig. 1C). The anterograde effective refractory period of the normal pathway could be compared in 14 patients (Cases 3, 4, 7, 8, 10 to 12, 15, 16, and 18 to 22), and increased from 255 ± 39 ms (range <160 to 300) before diltiazem to 319 ± 47 ms (range 220 to 370) after diltiazem ($p < 0.01$). The effects of diltiazem on the anterograde properties of the accessory pathway were variable. The longest atrial paced cycle length that induced block in the accessory pathway was compared in 7 patients (Cases 7, 8, 10, 11, and 21 to 23). It was 420 ± 164 ms (range <260 to 690) before and 397 ± 150 ms (range 260 to >730) after diltiazem (p = NS). The anterograde effective refractory period of the accessory pathway was compared in 7 patients (Cases 7, 9, 10, and 21 to 24) and was

TABLE I Electrophysiologic Findings Before and After Diltiazem in Group I Patients

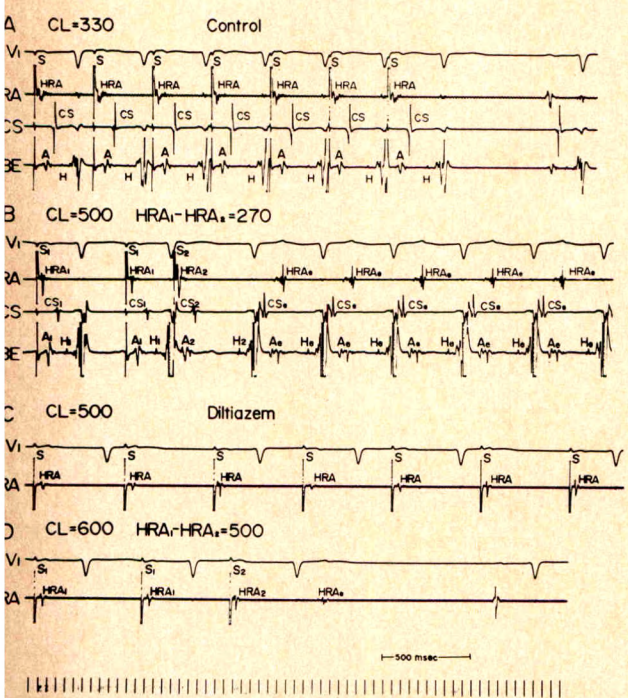
		PVST				Anterograde Properties (ms)						Retrograde Properties (ms)			
Case No.		Induction	CL (ms)	Sustainability	Weak Link	CL-APB	CL-AVB	ERP-AP	ERP-AVCS	ERP-At	Echo Zone	CL-VAB	ERP-VACS	ERP-Vt	Echo Zone
1	C	+	300	+	0	—	280	—	<260	190	320–260	<280	<250	200	360
	D	+	440	+	0	—	400	—	250	190	280	<300	310	240	—
2	C	+	450	+	0	—	360	—	340	250	400–350	<300	—	—	—
	D	+	410	+	0	—	360	—	—	—	—	<300	<240	<240	250–240
3	C	+	290	+	0	—	<240	—	<210	200	250–210	<280	<200	<190	230–200
	D	+	310	+	0	—	300	—	220	200	280–270	<300	240	200	—
4	C	+	420	+	0	—	400	—	300	230	500–310	<280	<230	220	250–230
	D	+	430	+	0	—	400	—	290	240	390–300	<280	280	220	—
5	C	+	370	+	0	—	330	—	230	180	460–260	<280	<190	<190	—
	D	+	430	0	Ant	—	500	—	—	230	540–240	<280	<210	200	—
6	C	+	290	+	0	<260	—	255	260	230	—	<260	<220	<220	220
	D	+	330	0	Ant	<260	—	<280	—	<270	—	<280	290	290	—
7	C	+	320	+	0	300	≥330	270	<250	240	270–250	280	<280	280	—
	D	+	445	0	Ret	330	≥330	310	>310	290	—	330	330	190	—
8	C	+	285	+	0	>690	<280	—	<160	150	250–160	<280	<200	<180	—
	D	Echo	—	—	Ant	460	≥460	420	360	240	420–370	<280	270	230	—
9	C	+	380	+	0	<300	—	270	≥270	260	—	<280	<270	<250	—
	D	Echo	—	—	Ant	<280	—	260	>260	250	—	<280	<290	<350	280
10	C	+	340	+	0	<260	300	260	260	140	—	<280	<210	200	280–260
	D	Echo	—	—	Ant	300	≥300	290	260	190	310–270	<280	<240	230	—
11	C	+	310	+	0	650	300	—	<280	250	310–290	<280	240	<240	—
	D	Echo	—	—	Ant	>730	360	—	320	<300	330	<280	250	<250	—
12	C	+	375	+	0	—	360	—	290	210	430–300	<280	290	<260	—
	D	Echo	—	—	Ant	—	460	—	370	240	460–380	280	300	<300	—
13	C	+	400	+	0	—	360	—	<350	<320	610–350	280	250	220	270–260
	D	Echo	—	—	Ant	—	400	—	—	—	—	280	250	220	260–250
14	C	+	260	+	0	—	250	—	<210	190	260–210	<300	<170	160	250–170
	D	Echo	—	—	Ant	—	460	—	<380	<380	460–390	<280	310	240	330–320
15	C	+	340	+	0	—	280	—	<220	200	260–230	<250	<230	230	—
	D	Echo	—	—	Ant	—	400	—	320	<300	350–330	300	310	<300	—
16	C	+	370	+	0	—	300	—	290	220	340–300	<330	250	200	240–230
	D	Echo	—	—	Ant	—	430	—	360	220	400–370	<280	260	<230	260–250
17	C	+	380	+	0	—	300	—	<220	210	280–240	<300	<220	<200	—
	D	Echo	—	—	Ant	—	500	—	—	<410	480–430	300	300	300	—
18	C	+	325	+	0	—	300	—	<260	250	340–260	<280	370	<370	—
	D	Echo	—	—	Ant	—	460	—	340	300	430–350	<300	300	<280	—
19	C	+	350	+	0	—	300	—	<275	240	—	280	270	200	—
	D	Echo	—	—	Ant	—	430	—	360	260	370	300	310	240	—
20	C	+	300	+	0	—	300	—	<250	<240	280–250	280	270	190	—
	D	0	—	—	—	—	360	—	370	270	—	300	290	220	—
21	C	+	290	+	0	280	210	260	<250	210	270–250	<280	<200	190	—
	D	0	—	—	—	260	≥260	260	≥260	230	—	<280	<220	<220	—
22	C	+	375	+	0	360	300	285	<270	260	300–270	<280	<250	240	—
	D	0	—	—	—	300	≥300	320	≥320	240	—	330	340	230	—
23	C	+	280	+	0	400	300	420	<270	260	330–270	<280	<280	270	—
	D	0	—	—	—	400	≥400	<340	—	330	—	300	330	240	—
24	C	+	300	+	0	<280	230	240	170	150	230–200	<270	220	210	—
	D	0	—	—	—	<280	—	<240	—	210	—	—	—	—	—

Ant = anterograde; C = control; CL = cycle length; CL-APB = the longest atrial paced cycle length that induced block in the accessory pathway; CL-AVB = the longest atrial paced cycle length that induced block in the normal pathway; CL-VAB = the longest ventricular paced cycle length that induced ventriculoatrial block; D = diltiazem; ERP-AP = the effective refractory period of the accessory pathway; ERP-At = the atrial effective refractory period; ERP-AVCS = the effective refractory period of the atrioventricular conducting system (normal pathway); ERP-VACS = the effective refractory period of the ventriculoatrial conducting system; ERP-Vt = the ventricular effective refractory period; 0 = no induction of paroxysmal supraventricular tachycardia (PVST), unable to sustain PSVT or no weak link; Ret = retrograde; + = induction of PSVT or ability to sustain PSVT; — = data not generated.

86 ± 60 ms (range 240 to 420) before and 289 ± 37 ms ange <240 to 340) after diltiazem (p = NS).

The longest ventricular paced cycle length that inuced 2° VA block (in the accessory pathway) could be ompared in 9 patients (Cases 7, 12, 13, 15, 17, 19, 20, 22, nd 23) and was 279 ± 12 ms (range <280 to 300) before nd 302 ± 17 ms (range <280 to 330) after diltiazem (p 0.02) (Fig. 2A and 2C). The retrograde effective reactory period of the VA conducting system (the accessory pathway) could be compared in 18 patients Cases 1, 3, 4, 6 to 8, 11 to 20, 22, and 23) and was 248 ± 4 ms (range <200 to 370) before and 293 ± 29 ms ange 240 to 340) after diltiazem (p <0.001) (Fig. 2B and E).

Effects on AV nodal reentrant tachycardia Table II, Cases 25 to 36; Fig. 3 and 4): In all 12 paents, sustained SVT could be induced before diltiazem. After diltiazem, sustained SVT could be induced in 4 patients (Cases 25 to 28), nonsustained SVT in 2 patients (Cases 29 and 30) (Fig. 3), a single AV nodal reentrant echo in 2 patients (Cases 31 and 32), and neither SVT nor an echo could be induced in 4 patients (Cases 33 to 36) (Fig. 4). In patients in whom nonsustained SVT or a single echo could be induced, the weak link occurred in the anterograde direction in 2 patients (Cases 29 and 32) (Fig. 3B), and the retrograde direction in 2 patients (Cases 30 and 31). In the 4 patients in whom neither SVT nor an echo could be induced, the weak link occurred in the retrograde direction. The cycle length of the SVT, which could be compared in 5 patients, lengthened in 3 patients (Cases 26, 28, and 30), remained unchanged in 1 patient (Case 25), and shortened in 1 patient (Case 27). Overall, the cycle length was



GURE 1. Recordings from Case 17 showing the induction of a single rioventricular (AV) reentrant echo after diltiazem and the effects of tiazem on anterograde AV conduction. Electrocardiographic V_1, high ght atrial electrogram (HRA), left atrial electrogram recorded from the ronary sinus (CS), and His bundle electrogram (HBE) are shown. HRA, S, A, and H represent, respectively, the high right atrial, left atrial, low ptal right atrial, and His bundle responses to the driven stimulus (S). HRA_e, CS_e, A_e, and H_e represent, respectively, high right atrial, left atrial, w septal right atrial, and His bundle responses during induced reentrant hoes or tachycardia, or both. HRA_1, A_1, and H_1 represent, respecely, high right atrial, low septal right atrial, and His bundle responses the basic driven stimulus (S_1). HRA_2, A_2, and H_2 represent, respecely, high right atrial, low septal right atrial, and His bundle responses the extrastimulus (S_2). The paper speed is 100 mm/s. **A,** 1:1 AV nduction at an atrial paced cycle length of 330 ms before diltiazem. the induction of sustained AV reentrant supraventricular tachycardia th an atrial extrastimulus before diltiazem. The atrial driven cycle ngth was 500 ms, and the coupling interval was 270 ms. **C,** 2° AV ock at an atrial paced length of 500 ms after diltiazem. **D,** the induction a single echo with an atrial extastimulus after diltiazem. The atrial ven cycle length was 600 ms and the coupling interval was 500 ms. e echo (HRA_e) was not followed by a QRS complex, suggesting an terograde weak link.

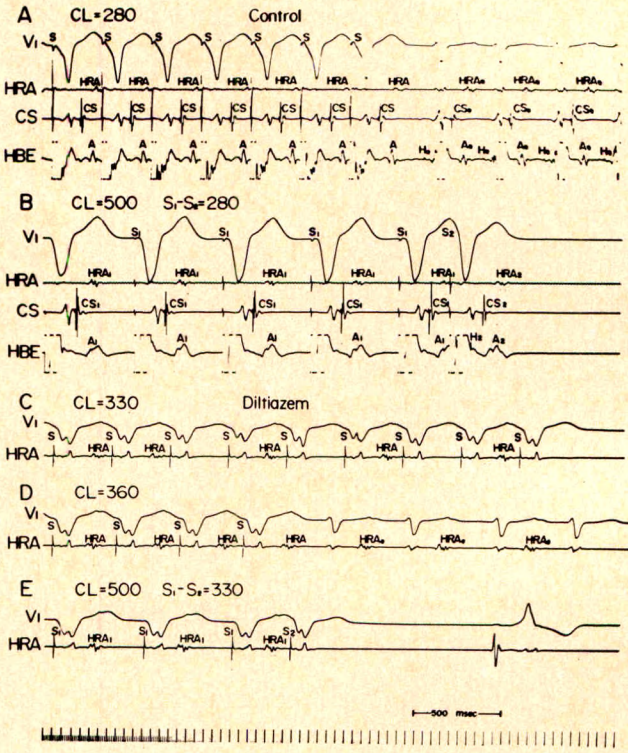
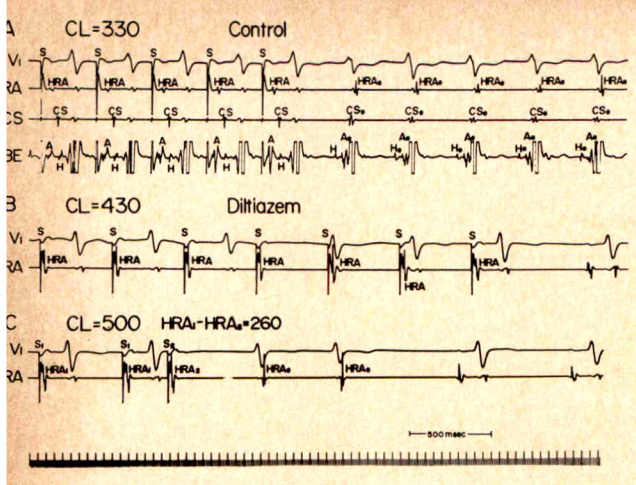


FIGURE 2. Recordings in Case 7 showing the induction of nonsustained atrioventricular (AV) reentrant supraventricular tachycardia (SVT) after diltiazem and the effects of diltiazem on retrograde accessory pathway conduction. **A,** the induction of sustained SVT after termination of rapid ventricular pacing at a paced cycle length of 280 ms before diltiazem. Note 1:1 ventriculoatrial (VA) conduction during ventricular pacing. **B,** the conduction of the ventricular extrastimulus to the atria through a left-sided accessory pathway at a coupling interval of 280 ms and a basic driven cycle length of 500 ms before diltiazem. CS_2 was activated earlier than both A_2 and HRA_2. **C,** the occurrence of 2° VA block after diltiazem at a ventricular paced cycle length of 330 ms. **D,** the induction of nonsustained SVT after diltiazem after the termination of rapid ventricular pacing at a paced cycle length of 360 ms. Termination of SVT occurred when the QRS complex was not followed by an atrial response, suggesting a retrograde weak link. **E,** the block of the ventricular extrastimulus to the atria after diltiazem at a coupling interval of 330 ms and a ventricular driven cycle length of 500 ms. Thus, the effective refractory period of the VA conducting system (the accessory pathway) was increased from <280 to 330 ms after diltiazem. Other abbreviations as in Figure 1.

TABLE II Electrophysiologic Findings Before and After Diltiazem in Group 2 Patients

Case No.		PSVT Induction	PSVT CI (ms)	PSVT Sustainability	PSVT Weak Link	Anterograde Properties (ms) CL-AVB	ERP-AVCS	ERP-At	Echo Zone	Retrograde Properties (ms) CL-VAB	ERP-VACS	ERP-Vt	Echo Zone
25	C	+	450	+	0	360	295	260	—	330	<270	265	430–275
	D	+	450	+	0	360	<270	240	—	330	<250	240	360–270
26	C	+	390	+	0	300	275	220	370–270	280	<250	240	—
	D	+	410	+	0	330	<300	270	390–300	<280	<220	210	—
27	C	+	420	+	0	360	340	<300	480–340	300	<270	270	—
	D	+	375	+	0	360	260	<260	390–270	300	<220	200	—
28	C	+	440	+	0	330	<270	230	—	360	320	230	—
	D	+	570	+	0	545	—	—	—	460	—	—	420
29	C	+	370	+	0	300	<230	180	280–230	<280	200	200	—
	D	Echoes	—	0	Ant	430	260	200	360–270	430	400	190	—
30	C	+	285	+	0	250	<150	140	220–150	<280	<220	210	—
	D	+	340	0	Ret	360	<220	210	280–220	360	370	<290	—
31	C	+	365	+	0	280	<250	240	350–250	300	320	<300	—
	D	Echo	—	—	Ret	360	<260	260	315–260	400	430	<360	—
32	C	+	400	+	0	360	290	280	450–300	300	<200	190	—
	D	Echo	—	—	Ant	545	—	—	—	330	250	<220	—
33	C	+	325	+	0	330	<250	225	370–250	330	<225	215	—
	D	0	—	—	Ret	500	—	—	—		(no VA conduction)		—
34	C	+	240	+	0	<280	<200	180	270–200	<280	<240	200	—
	D	0	—	—	Ret	400	250	210	—		(no VA conduction)		
35	C	+	420	+	0	360	<270	220	380–270	300	<260	290	—
	D	0	—	—	Ret	545	—	—	—	545	—	—	—
36	C	+	420	+	0	400	310	220	390–320	300	<240	230	—
	D	0	—	—	Ret	545	—	220	—		(no VA conduction)		—

Abbreviations as in Table I.



IGURE 3. Recordings in Case 29 showing the induction of nonsustained rioventricular (AV) nodal reentrant echoes after diltiazem and the ffects of diltiazem on anterograde slow-pathway conduction. **A,** the duction of sustained supraventricular tachycardia (SVT) after termiation of rapid atrial pacing at a paced cycle length of 330 ms before ltiazem. Note 1:1 slow pathway conduction during atrial pacing. **B,** e occurrence of 2° AV block at an atrial paced cycle length of 430 s, reflecting an increased anterograde slow pathway refractoriness ter diltiazem. **C,** the induction of nonsustained echoes with an atrial xtrastimulus after diltiazem. The atrial driven cycle length was 500 s and the coupling interval was 260 ms. The echoes were terminated ith HRA_e not being followed by a QRS complex, suggesting an anrograde weak link. Other abbreviations as in Figure 1.

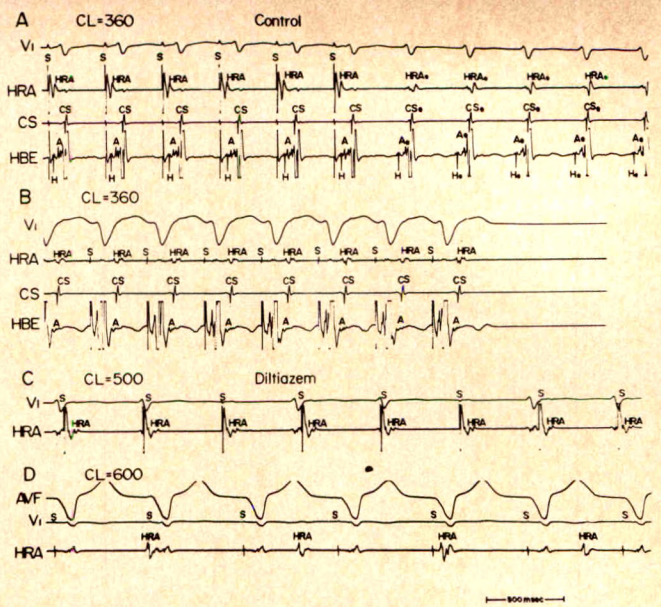


FIGURE 4. Recordings in Case 33 showing effects of diltiazem on the anterograde slow pathway and the retrograde fast pathway conduction. **A,** the induction of sustained atrioventricular (AV) nodal reentrant supraventricular tachycardia (SVT) after termination of rapid atrial pacing at a paced cycle length of 360 ms before diltiazem. Note 1:1 slow pathway conduction during rapid atrial pacing. **B,** 1:1 ventriculoatrial (VA) conduction during rapid ventricular pacing at a paced cycle length of 360 ms before diltiazem. **C,** 2° AV block at an atrial paced cycle length of 500 ms after diltiazem, reflecting an increased anterograde slow pathway refractoriness. **D,** no VA conduction at a ventricular paced cycle length of 600 ms after diltiazem, suggesting an increased retrograde fast pathway refractoriness. Other abbreviations as in Figure 1.

97 ± 60 ms (range 285 to 450) before and 429 ± 79 ms range 340 to 570) after diltiazem (p = NS).

The longest atrial paced cycle length that induced 2° V block could be compared in all 12 patients and increased from 326 ± 42 ms (range <280 to 400) to 440 ± 5 ms (range 330 to 545) after diltiazem (p <0.001) (Figs. A and 3B, 4A and 4C). The anterograde effective refractory period of the AV conducting system (reflecting that f the slow pathway) could be compared in only 4 patients (Cases 25, 27, 29, and 34) and was decreased in 1 atient (Case 25) and increased in 3 (Cases 27, 29, and 4). In 5 patients (Cases 28, 32, 33, 34, and 35), the longest atrial paced cycle length that induced AV block fter diltiazem was longer than the control basic driven ycle length.

The longest ventricular paced cycle length that induced 2° VA block could be compared before and after iltiazem in 9 patients (Cases 25 to 32 and 35), and increased from 303 ± 25 ms (range <280 to 360) to 382 ± 0 ms (range <280 to 545) after diltiazem (p <0.05). In he remaining 3 patients (Cases 33 to 35), no VA conduction was noted after diltiazem (Fig. 4B and 4D). The ffective refractory period of the VA conducting system ould be compared in 4 patients (Cases 29 to 32) and was ncreased in all 4.

Other observations: On the whole, the sinus cycle ength lengthened from 694 ± 104 to 779 ± 145 ms after iltiazem (p <0.001). The systolic pressure decreased om 131 ± 22 to 121 ± 16 mm Hg after diltiazem (p 0.05), whereas the diastolic pressure remained unhanged and was 85 ± 14 before and 80 ± 13 mm Hg after diltiazem (p = NS). The atrial effective refractory period increased from 211 ± 39 to 239 ± 35 ms after diltiazem (p <0.001). The ventricular effective refractory period was 219 ± 31 before and 221 ± 17 ms after diltiazem (p = NS).

Plasma diltiazem concentration was measured in 29 patients and was 156 ± 75 ng/ml (range 24 to 320). There was no difference in drug level among those patients with or without induction of sustained SVT.

Follow-up data: Fifteen patients were discharged on the same dosage of oral diltiazem and followed up in the clinic 5 ± 3 months. Of the 2 patients (Cases 25 and 26) in whom sustained SVT could be induced after diltiazem, both experienced 3 episodes of sustained SVT that required hospital visits for termination during the follow-up period. Of the 13 patients (Cases 8, 9, 12, 15, 16, 22 to 26, 33 to 35, and 39) in whom sustained SVT could not be electrically induced after diltiazem, only 1 patient (Case 22) experienced palpitations (4 episodes) during the follow-up period. The frequency of SVT in these 13 patients ranged from 1 to 4 attacks/month (mean 1.7/month) before diltiazem therapy. All 15 patients tolerated the medication well and experienced no major side effects.

Discussion

Slow-channel antagonists, such as verapamil, diltiazem, and nifedipine, are effective antianginal agents,

particularly in treating the vasospastic type of angina pectoris. Verapamil is also effective in controlling tachyarrhythmias involving the AV node.[18–22] Microelectrophysiologic studies have shown that diltiazem at a therapeutic concentration decreases the action potential plateau and shortens the action potential duration in both ventricular muscles and Purkinje fibers without significantly affecting the maximum upstroke velocity and the resting membrane potential.[23,24] In clinical and animal studies, diltiazem depresses AV nodal function with prolongation of AV nodal conduction time and both the functional and the effective refractory periods.[1–4] It reduces the sinus rate, but has no significant effects on the atria, the His-Purkinje system, and the ventricles. Limited clinical studies have shown that intravenous diltiazem terminates paroxysmal SVT and slows the ventricular rate in patients with atrial fibrillation.[5–7] The elimination half-life of intravenous diltiazem was shown to be 1.9 hours.[8,9,25] After oral administration of the release-controlled tablet, the peak plasma concentration is achieved within 3 to 5 hours, and the elimination half-life is approximately 4.5 hours.[9,25]

The findings of this study on oral diltiazem in patients with AV reentrant tachycardia showed that diltiazem depressed anterograde normal pathway conduction (AV node) and lengthened the AV nodal conduction time. However, slowing the AV nodal conduction time did not negate the beneficial effect of prolonging the AV nodal effective refractory period in most patients. Moreover, the AV node was also depressed in such a way that an appropriate AV nodal delay (in patients without preexcitation) or the normal pathway conduction (in patients with preexcitation) could not be achieved, so that echoes and tachycardia were not induced after diltiazem. These observations are consistent with the previous observations of Wakasa et al[5] and Rozanski et al.[6] Although diltiazem had no significant effect on anterograde accessory pathway conduction, it had a mild depressant effect on retrograde accessory pathway conduction, as suggested by the prolongation of both the longest ventricular paced cycle length that induced VA block and the effective refractory period of the VA conducting system. The significance of this latter finding requires further clarification.

In patients with AV nodal reentrant tachycardia, diltiazem depressed anterograde conduction (reflecting the slow-pathway conduction) as suggested by prolongation of the longest atrial paced cycle length that induced AV block. It also depressed retrograde conduction (reflecting the fast-pathway conduction) as suggested by prolongation of the longest ventricular paced cycle length that induced VA block. Wakasa et al[5] showed that the AV nodal conduction curve became continuous after diltiazem in 3 of 5 patients with discontinuous AV nodal conduction curves, suggesting increased anterograde slow pathway refractoriness. Rozanski et al[6] reported termination of tachycardia in 4 patients with AV nodal reentrant tachycardia occurring in the anterograde direction after intravenous diltiazem, suggesting increased anterograde pathway refractoriness. They also demonstrated a depressant effect of diltiazem on retrograde pathway conduction as assessed by ventricular or programmed stimulation. Studies of procainamide, quinidine, and disopyramide have shown that type I antiarrhythmic agents have a specific depressant effect on the retrograde fast AV nodal pathway.[26–28] The present study further suggests that the retrograde AV nodal pathway (the fast pathway) is subject to the influence of slow-channel antagonists. These findings imply that the retrograde fast AV nodal pathway may possess tissues that have the characteristics of both fast- and slow-channel responses.

Oral diltiazem caused a minor but significant lengthening of the sinus cycle length and a mild reduction in systolic pressure. The atrial effective refractory period increased slightly but significantly. This latter finding might be related in part to the observed depressant effect of diltiazem on retrograde accessory pathway conduction, as the measurement of the retrograde accessory pathway conduction with ventricular or programmed stimulation was dependent on the atrial response. Nevertheless, we could not exclude the possibility of an error in the measurement of the atrial effective refractory period resulting from poor contact of the catheter with the atrial wall.

Our follow-up data support the hypothesis that oral diltiazem is effective in preventing the recurrence of paroxysmal SVT and that electrophysiologic study may predict subsequent clinical responses. Our studies were performed 2 hours after only 3 doses of diltiazem. A steady-state drug level might not have been achieved in some patients. Perhaps the long-term effects of diltiazem on SVT are better than our studies suggest.

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Effect of Procainamide on Dispersion of Ventricular Refractoriness

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Ventricular arrhythmias after Q-T prolongation by drugs could result from a nonhomogeneous increase in refractoriness (dispersion). Dispersion of effective refractory periods (ERP) was measured before and after infusion of 1 g of procainamide using twice-threshold extrastimuli applied in sinus rhythm and with 500 ms ventricular drive cycle length at 3 right ventricular sites (2 patients) or 2 right and 1 left ventricular site (10 patients). Procainamide prolonged ERP. In drive, average ERP was 247 ± 5 ms (standard error of the mean) before and 277 ± 7 ms after procainamide ($p < 0.001$). The Q-T interval was prolonged by 50 ms in drive ($p < 0.001$), but Q-T prolongation did not reflect the increased ERP ($r = -0.05$). However, procainamide did not alter measured dispersion (54 ± 16 to 44 ± 14 ms in sinus, 48 ± 14 to 47 ± 13 ms in drive). Polymorphic ventricular tachycardia (VT) was induced in 6 patients in whom drive itself generally failed to reduce dispersion, and failure to induce tachycardia or shorter runs after procainamide was associated with narrowed dispersion. Polymorphic VT was not induced after procainamide in 2 patients with clinical episodes of torsades de pointes caused by type I agents. The mechanism of torsades de pointes was not explained by dispersion of refractoriness or by polymorphic VT initiated by premature beats after a type I drug.

Type I antiarrhythmic drugs cause Q-T prolongation and are sometimes associated with worsened or new ventricular tachyarrhythmias.[1,2] The latter might be explained by prolonged refractoriness signaled by the long Q-T interval or by nonuniform lengthening of refractoriness (dispersion), with asynchrony of repolarization marked by the long Q-T interval.[3] We examined Q-T intervals and dispersion of refractoriness as altered by procainamide (PA) and their relation to polymorphic ventricular tachycardia (VT), using extrastimulation at 3 disparate ventricular sites.

Methods

Twelve patients underwent ventricular extrastimulation in a nonsedated postabsorptive state for documented or suspected ventricular tachyarrhythmias after giving informed consent. All antiarrhythmic drugs were discontinued at least 5 half-lives before study and none of the patients was receiving beta-blocking agents. Digitalis and diuretics were withheld the morning of study. Clinical characteristics of the patients (Table I) were organized on the basis of torsades de pointes and subsequently induced polymorphic (VT). Two patients had torsades de pointes while receiving type I antiarrhythmic drugs, but the QT_c ($QT/\sqrt{RR}$) was ≤0.45 second in all patients at baseline. Six had coronary artery disease.

A quadripolar pacing catheter with an interelectrode distance of 1 cm was positioned at the right ventricular apex. Bipolar recordings were made from the proximal poles at filter settings of 30 to 500 Hz, using an Electronics for Medicine VR12 oscilloscopic recorder. Surface leads I, aVF, and V_1 were recorded as well. Additional bipolar pacing catheters were positioned at the right ventricular outflow tract and also within the left ventricle (10 patients) or at an additional right ventricular site (2 patients). Twice-threshold 2-ms extrastimuli were decrementally applied after each 8 sinus beats and 8 beats of ventricular drive at a cycle length of 500 ms using a Medtronics 5325 or a specially modified Bloom stimulator (Bloom, Reading, Pennsylvania)

One gram of intravenous PA was then infused at 100 mg/min or slower if hypotension developed. Extrastimulation was repeated within 10 minutes at the same 3 sites without catheter repositioning and blood was drawn for serum PA determination immediately thereafter.

The effective refractory period (ERP) was the longest coupling interval at which extrastimulation did not result in a propagated response. Dispersion of ERP was the range of effective refractory periods at the 3 sites. The Q-T interval, measured from the onset of the QRS to the point where the descending portion of the T wave met the isoelectric line, was

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TABLE I Clinical Characteristics of Patients Studied

Case	Age (yr) & Sex	Structural Heart Disease	Clinical Ventricular Arrhythmias	QT_c
1	51M	CAD	NSVT	0.36
2	56M	CAD	None	0.42
3	60F	CAD	None	0.38
4	56M	CAD	NSVT	0.43
5	37F	MVP	Couplets	0.35
6	60M	None	Torsades	0.43
7	57F	CAD	Torsades	0.44
8	76M	CAD	NSVT	0.43
9	85F	None	NSVT	0.37
10	58F	None	NSVT	0.45
11	64M	CAD	NSVT	0.38
12	32F	None	NSVT	0.42

CAD = coronary artery disease; MVP = mitral valve prolapse; NSVT = nonsustained ventricular tachycardia, diagnosed as torsades (torsades de pointes) if sufficiently sustained to demonstrate sinusoidal rotation and return to original electrical axis; $QT_c = QT/\sqrt{RR}$.

corrected for sinus rate by the relation $QT_c = QT/\sqrt{RR}$.[4] Polymorphic VT was defined as multiform VT with a gradually changing electrical axis, sometimes resembling torsades de pointes. Data were compared before and after PA using a paired t test, and changes were related and compared with serum PA by linear regression.

Results

PA prolonged ERP (Table II). In sinus rhythm, the average ERP was lengthened by PA from 278 ± 8 ms (standard error of the mean) to 288 ± 8 ms (difference not significant [p = NS]) and the longest ERP from 307 ± 16 to 312 ± 12 ms (p = NS). The changes were small but cycle length was abbreviated, presumably in response to the decreased blood pressure after the infusion. With cycle length fixed at 500 ms by ventricular drive (Fig. 1), PA prolonged average ERP from 247 ± 5 to 277 ± 7 ms (p <0.001) and longest ERP from 276 ± 14 to 304 ± 13 ms (p <0.001). Dispersion of ERP was not widened by PA (from 54 ± 16 to 44 ± 14 ms in sinus rhythm, from 48 ± 14 to 47 ± 13 ms in drive; p = NS).

The average serum PA concentration was 5.4 ± 3 μg/ml (± standard deviation). Neither the change in average ERP nor that in dispersion correlated with serum PA (r = 0.11, −0.48).

Applying extrastimuli in 10-ms decrements, and anticipating a 15-ms increase in dispersion (the longest ERP had increased in drive an average of 28 ms), there is a 5% chance that we failed to detect an increase by evaluating only 12 patients. Alternatively, there is a 50% chance that we failed to detect a 6.5-ms increase in dispersion by studying only 12 patients.

Despite a faster heart rate and a reduction in dispersion, QT_c prolonged after PA, from 0.40 ± 0.01 to 0.48 ± 0.01 second (p <0.001). In drive, the Q-T interval lengthened from 0.38 ± 0.003 to 0.43 ± 0.01 second (p <0.001), but Q-T prolongation did not reflect the increased ERP (r = −0.05).

Polymorphic VT, sometimes resembling torsades de pointes, was induced in drive in 6 patients before PA was given. Of the 2 patients with spontaneous torsades de pointes while receiving type I antiarrhythmic drugs (Table I), only 1 had inducible polymorphic VT. After PA, polymorphic VT could not be induced in 3 of 6 patients (including the patient with spontaneous torsades de pointes presumably resulting from PA) and was briefer than that before the drug in the other 3. Patient 5 (Table II) had 37 beats of polymorphic VT induced using a drive cycle length of 600 ms, but only 3 beats after PA. The patient with clinical torsades de pointes presumably from quinidine did not have induced polymorphic VT either before or after PA. Polymorphic VT was induced in patients in whom drive itself generally failed to reduce dispersion (62 ± 25 ms sinus rhythm, 63 ± 27 ms with 500 ms cycle length drive). Prevention of induction or briefer polymorphic VT after PA was associated with decreased dispersion (in all, by 22 ms in sinus rhythm, by 8 ms in drive [Fig. 1]). In those without polymorphic VT, drive reduced dispersion by 24 ms, but PA did not (dispersion increased an average of 4 ms in sinus rhythm). None of these changes was

TABLE II Refractory Periods and Induced Arrhythmias

	Basal					Procainamide (1 g)				
Case	ERP,NSR (mean [ms])	ERP,NSR (range [ms])	ERP,500 (mean [ms])	ERP, 500 (range [ms])	Induced VT	ERP,NSR (mean [ms])	ERP,NSR (range [ms])	ERP,500 (mean [ms])	ERP,500 (range [ms])	Induced VT
1	303	180	283	180	PVT(13)	287	150	300	170	PVT(4)
2	240	20	213	10	PVT(7)	250	0	247	10	. . .
3	257	30	243	40	PVT(7)	270	20	253	20	. . .
4	253	30	243	30	PVT(8)	273	10	280	20	PVT(3)
5	290	50	250	20	. . .	280	20	263	20	PVT(3)
6	273	60	273	100	PVT(7)	263	40	280	100	. . .
7	290	20	260	30	. . .	333	40	313	20	. . .
8	283	10	247	20	VT(a)	333	30	307	30	. . .
9	270	30	223	10	. . .	297	10	267	10	. . .
10	327	130	243	20	. . .	290	100	245	10	. . .
11	267	30	247	40	. . .	287	50	297	60	. . .
12	VB	VB	243	70	. . .	. . .	. . .	277	100	. . .
Mean	278	54	247	48	. . .	288	44	277	47	. . .
SEM	7.5	16	5.4	14	. . .	7.9	14	6.6	13	. . .

ERP,NSR = effective refractory period, normal sinus rhythm; ERP,500 = effective refractory period, ventricular drive at 500 ms cycle length; PVT = polymorphic ventricular tachycardia (maximum number of beats induced); SEM = standard error of the mean; VB = ventricular bigeminy; VT = ventricular tachycardia; (a) uniform sustained ventricular tachycardia. Patient 5 had prolonged PVT induced in the basal state at a drive cycle length of 600 ms (see text).

statistically significant, but possibly induction of polymorphic VT by postdrive extrastimuli reflected failure of drive to lessen dispersion, and less polymorphic VT after PA reflected narrowing of dispersion.

Discussion

Type I antiarrhythmic drugs may prevent ventricular tachyarrythmias partly by prolonging refractoriness. Differing effects on the diverging pathways of a potentially reentrant circuit can prevent reentry by making refractoriness uniform, converting unidirectional block to homogeneous propagation or to complete block. However, a drug prolonging refractoriness could have more effect on pathways already more refractory (increased sensitivity to the drug when there already is retarded repolarization). Further increased disparity of refractoriness would facilitate reentry, and we have found facilitated VT induction with widened tachycardia zones in response to extrastimulation in many patients with chronic recurrent VT.[5] This finding could explain arrhythmias associated with prolonged repolarization, such as torsades de pointes. Marked increased dispersion of refractoriness has been described in congenital Q-T prolongation syndromes.[6] Because type I antiarrhythmic agents can cause torsades de pointes when there is Q-T prolongation, we attempted to determine if these drugs can have a nonuniform effect on refractoriness to explain this arrhythmia.

PA prolongs ventricular refractoriness[7] and Levites et al[8] found PA to preferentially prolong refractory periods of the acutely injured canine ventricle, thereby reducing dispersion because ischemia shortened refractory periods. Michelson et al[9] studied 9 canine infarctions after 3 to 30 days, more closely resembling those of our patients with chronic ischemic disease. The dogs had inducible VT because of nonuniform injury caused by coronary reperfusion, but less inducible VT when PA prolonged refractoriness. However, in this chronic infarction model, PA did not consistently alter dispersion. Because we studied patients, we tested fewer sites, at longer basic cycle lengths, and selected patients without sustained arrhythmias.

Myerburg et al[10] found, in injured cat myocardium, that PA had its greatest effect when repolarization was shorter and its least effect when repolarization was longer. Action potential duration from healed (2 to 4 month old) myocardial infarction was longer than normal cells and prolonged after PA to a *lesser* extent than normal. Because tetrodotoxin affected both kinds of cells equally, this effect was not due to impaired delivery. ERP changes paralleled action potential changes, and the decreased differences after PA (decreased dispersion) correlated with loss of ability to induce sustained arrhythmias.

Induction of polymorphic VT analogous to torsades de pointes was not facilitated in our patients when PA prolonged their ERP and Q-T intervals, confirming the report of Horowitz et al.[11] Despite Q-T prolongation, PA actually tended to abbreviate dispersion measured in sinus rhythm when polymorphic VT became noninducible, more so than could be explained by a chronotropic effect from decreased blood pressure on its

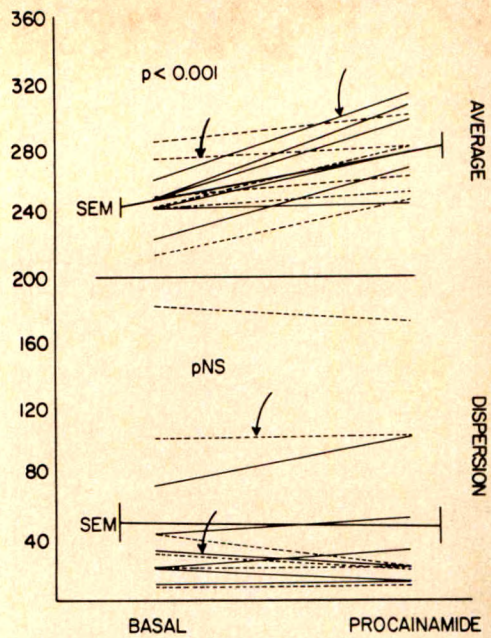

FIGURE 1. Average (**upper lines**) and dispersion (range, **lower lines**) of ventricular refractory periods before and after infusion of 1 g of procainamide. Mean and standard error of the mean are shown. Data refer to effective refractory periods measured with a ventricular drive cycle length of 500 ms. Average effective refractory period was prolonged ($p < 0.001$), but dispersion of refractoriness was not. The **dashed lines** indicate patients in whom polymorphic ventricular tachycardia was induced before procainamide, and the **arrows** refer to patients with clinical episodes of torsades de pointes.

infusion. That induction of polymorphic VT was not facilitated when PA prolonged the Q-T interval is difficult to relate to the mechanism of torsades de pointes because polymorphic VT is often not induced in patients with clinically recorded torsades de pointes.[12] However, when PA lengthened refractoriness and the Q-T interval, we did not detect widened dispersion of the ERP, even in patients with a history of torsades de pointes or previously induced polymorphic VT. This finding fails to substantiate the thesis that dispersion of refractoriness is a mechanism for torsades de pointes caused by type I agents, despite dispersion detected in patients with congenital torsades.[6]

We examined only 2 patients with torsades de pointes caused by drugs and perhaps measured an insufficient number of sites. Therefore, we may have failed to test those specific abnormal locations most sensitive to PA or with the longest ERP, that could respond to PA in an exaggerated fashion and result in marked dispersion. However, if the polymorphic VT we induced by extrastimulation was reentrant, the implication is that we did stimulate sites with sufficiently long ERP to permit unidirectional block. We found these sites with longer ERP not to be more sensitive to PA, consistent with Myerburg's observations[10] that sites with longer ERP are *less* sensitive to PA.

Thus, PA ameliorated induced polymorphic VT. Q-T prolongation by the drug did not signal further dispersion of the refractoriness we measured. These results might be unique to PA and cannot be extrapolated to

uinidine or disopyramide without separate trials. erhaps torsades de pointes is more commonly reported ith quinidine because quinidine *does* widen dispersion. lowever, we did not explain the mechanism of torsades e pointes by widening of dispersion or by polymorphic T in response to extrastimuli after a type I agent.

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Exercise-Induced Bundle Branch Block

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Exercise-induced bundle branch block (BBB) is poorly understood. An investigation was made of its clinical, electrocardiographic, coronary angiographic, and myocardial scintigraphic characteristics, with follow-up data in 16 patients, aged 59 ± 9 (mean ± standard deviation) years, 11 who had left BBB and 5 who had right BBB. Fourteen had a preexisting baseline electrocardiographic abnormality; 11 had either incomplete BBB or nonspecific intraventricular conduction delay. Heart rates at onset of exercise BBB varied from 70 to 166 beats/min and in 9 patients the rates at BBB onset and offset appeared to be related, occurring within 8 beats/min of each other. Coronary artery disease (CAD) was diagnosed in 10 patients, cardiomyopathy in 2, and probable coronary spasm in 2. One patient had ventricular arrhythmias of uncertain origin, and 1 appeared to have no cardiac disease. Three patients had reversible thallium perfusion defects consistent with ischemia concurrent with developing BBB. The 3 patients in whom exercise BBB persisted all had CAD. Over a mean of 28 months of follow-up, only 1 patient had a morbid cardiac event—nonfatal myocardial infarction—and 2 died from noncardiac causes. Thus, exercise BBB primarily occurs in the context of cardiac disease, most commonly CAD, and concurrent ischemia may be demonstrable; the presence of "rate relation" does not militate against CAD.

There are well-recognized electrocardiographic (ECG) responses to myocardial ischemia, but little information other than case reports is available on the diagnostic and prognostic significance of exercise-induced bundle branch block (BBB). We assessed the clinical data, available coronary angiographic and scintigraphic information, and follow-up in 16 patients with this phenomenon.

Methods

Patient selection and exercise testing: Of 4,100 subjects who had exercise tests between February 1977 and February 1982, 16 (0.39%) had exercise-induced complete left or right BBB. Twelve were men and 4 were women, aged 45 to 76 years (mean 59 ± 9). Fourteen had maximal exercise with the standard and 2 with the modified Bruce protocol.

BBB criteria: *Left:* QRS ≥ 0.13 second; absent septal q; small or absent R waves with wide S waves in medial precordial leads.

Right: QRS ≥ 0.12 second; R′ in V_1 after 0.08 second; broad S in lead 1 and lateral precordial leads.

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Coronary angiography and myocardial scintigraphy: Six patients had coronary angiography. Significant disease was defined as ≥50% luminal reduction in a major branch.

Eight patients had thallium-201 scintigraphy; perfusion was analyzed regionally as normal, reversible (consistent with ischemia), or irreversible (consistent with scarring).

Follow-up: Follow-up data were obtained from patients and physicians. Morbid cardiac events were defined as those that required hospitalization of the patient.

Results

Table I lists patient profiles, medications, test indications, baseline electrocardiograms, and exercise data.

Eleven patients had left BBB and 5 had right BBB during exercise.

Left BBB (11 patients): Nine patients had a prior ECG abnormality: 6 either incomplete left BBB or nonspecific intraventricular conduction delay (IVCD) (QRS ≥ 0.10 second), 1 nonspecific ST-T changes, 1 left ventricular hypertrophy, and 1 left-axis deviation and old inferior infarction.

Heart rates at left BBB onset varied from 70 to 166 beats/min and at offset from 66 to 131 beats/min. In 7 cases, offset rate was within 8 beats of onset rate. In 3 cases, onset and offset rates differed >25 beats. In 1 case, left BBB persisted beyond the recovery phase. Exercise was stopped in 1 patient because of onset of left

TABLE I Clinical Data

Case	Age (yr) & Sex	Medications	Indication for Test	Pretest ECG	Exercise BBB	HR at BBB Onset (beats/min)	HR at BBB Offset (beats/min)	Test End Point	Final Diagnosis
1	61M	N	AP (HT)	IVCD	Left	92	85	AP	CAD
2	72M	M, quinidine	Palpitations (HT)	IVCD, LAD	Right	130	100	F, D	VA
3	45M	P	Chest pain	IVCD, LVH	Left	95	90	F	PMD
4	63M	N, P, T	AP (MI × 2)	IVCD	Left	101	72	F, D	CAD
5	49M	Disopyramide	Chest pain	Normal	Left	166	131	Target HR	Normal
6	55M	N	AP (MI)	Inc. LBBB	Left	96	88	Leg fatigue	CAD
7	55M	P, T	AP (HT)	Inc. LBBB, PMI	Right	77	Persisted	F, leg pain	CAD
8	67M	N, tolbutamide	AP (MI)	Inc. RBBB, LAD	Right	100	Persisted	F	CAD
9	53F	N, P, furosemide	AP	ST-T changes	Left	85	82	D	Cor spasm
10	51F	T, M	AP (HT)	IVCD	Right	85	85	D	Cor spasm
11	66F	...	AP, D	Normal	Left	70	66	D	CAD
12	60M	N, P	AP (MI)	Inc. RBBB, LAD	Right	*75–115	75–115	Target HR	CAD
13	55M	N, P	Chest pain	LVH	Left	72	72	LBBB onset	PMD
14	64M	P	AP (HT)	IVCD, LAD	Left	90	Persisted	AP	CAD
15	48M	N, P	AP (MI)	IVCD, LAD, PLMI	Left	138	88	D	CAD
16	76F	N, cimetidine	AP (MI)	LAD, MI	Left	*74–128	74–128	Target HR	CAD

* The exact rates of onset and offset of exercise BBB in these 2 patients could not be determined, but are known to be within 8 beats/min of each other.

AP = angina pectoris; BBB = bundle branch block; CAD = coronary artery disease; Cor spasm = coronary artery spasm; D = dyspnea; ECG = electrocardiogram; F = fatigue; HR = heart rate; HT = prior hypertension; Inc. = incomplete; IVCD = intraventricular conduction delay; LAD = left-axis deviation; LVH = left-ventricular hypertrophy; M = methyldopa; MI = prior myocardial infarction; N = nitrates; P = propranolol; PLMI = posterolateral myocardial infarction; PMD = primary myocardial disease; PMI = posterior myocardial infarct; T = thiazide diuretic; VA = ventricular arrhythmias.

BBB. The onset rate of left BBB displayed no obvious relation to the maximum heart rate achieved with symptom-limited testing. In 4 patients, onset rate was ≤7 beats of maximum rate; 7 patients exercised to 25 to 60 beats/min higher than the onset rate of left BBB.

Right BBB (5 patients): All 5 patients had a prior electrocardiographic abnormality, 3 incomplete right BBB and 2 IVCD. Onset rates of right BBB varied from 7 to 130 beats/min. In 2 patients, BBB persisted past the recovery phase and in 3, right BBB offset occurred at 85 to 100 beats/min; in 2 of them, onset and offset rates were almost identical. One patient had right BBB several seconds before the end of the test; the other 4 reached 23 to 61 beats/min higher than at BBB onset.

There were no apparent differences between patients who had left versus right BBB with regard to age, sex, and clinical characteristics.

Coronary angiography: Angiography was performed in 6 patients, 4 with exercise left BBB and 2 with right BBB. Two patients had severe 3-vessel coronary artery disease (CAD) with diminished left ventricular function. One (Patient 14) had intermittent left BBB during contrast injection. One patient with exercise right BBB (Patient 7) had right coronary disease—50% proximal stenosis and 90% distal stenosis near the origin of the atrioventricular nodal artery. Patient 13 had normal coronary arteries but mild anterolateral left ventricular hypokinesia. He had left ventricular hypertrophy on the resting electrocardiogram and a normal echocardiogram and is regarded as having primary myocardial disease. Left BBB developed several times during catheterization, apparently related to positional changes and contrast injection; heart rates for left BBB onset and offset were not recorded. Two patients had

Myocardial scintigraphy: Six patients, 4 with left and 2 with right exercise BBB, had exercise thallium-201 myocardial scintigraphy. Three had reversible perfusion defects, 2 of which were associated with additional irreversible defects. Ischemic areas were posterolateral in 1 and anteroseptal in 2; 1 (Patient 5) had a normal study and 2 had irreversible perfusion defects only, 1 septal and 1 apical.

Follow-up: Patients were followed up for 7 to 69 months (mean 28). Two died, 1 at 7 months after exercise testing from carcinoma. He had a previous myocardial infarction. The other, who also had had a previous infarction, died from glioma 32 months after testing. Neither had any morbid cardiac events between exercise testing and death. Of the remaining 14 patients, Patients 4 and 14 had coronary bypass shortly after testing without postoperative morbid cardiac events. One patient (Patient 16) had an infarct during follow-up study. Three patients, all with documented CAD, have stable angina.

In summary, clinical and investigational data yielded diagnoses of CAD in 10 patients and myocardial disease in 2. Two had anginal pain and fluctuating ST-T changes but normal coronary angiograms, suggesting coronary spasm (heightened by an abnormal exercise thallium scan in 1). One patient (Patient 2) had ventricular arrhythmias without other evidence of cardiac disease. Only 1 was considered normal.

Discussion

There are very few data, and thus there is no consensus, regarding the significance of exercise-induced complete BBB. This is surprising, as BBB renders the ECG response to exercise inconclusive, producing a diagnostic and management dilemma.

Our study, to our knowledge the largest reported

What are the clinical and ECG characteristics of patients with exercise-induced BBB? Does it represent a hitherto uncharacterized response to ischemia? Is it more prevalent in patients with than without CAD, or is it a "rate-related" electrical phenomenon not necessarily occurring in the context of CAD? What is its prognostic significance?

Compared with the scarce data concerning exercise BBB, some information is available on intermittent BBB unrelated to exercise. Coronary angiography in patients with intermittent BBB demonstrates both normal and diseased coronary arteries. Lewis et al[1] reported on 12 patients with left BBB; of 4 with intermittent left BBB, 2 had significant CAD, 1 normal coronary arteries, and 1 patent ductus. In another report,[2] 5 had normal coronary arteries, 1 significant CAD, and another idiopathic cardiomyopathy. In another series,[3] among 5 patients with intermittent left BBB, 3 had normal coronary arteries and 2 had single-vessel CAD. Scintigraphy in this study, using rubidium-81 and potassium-43, produced a number of false-positive resting perfusion scans, which returned to normal with exercise in patients with angiographically normal coronary arteries versus those with CAD. Yet there were some equivocal exercise scintigraphic results. Of 8 patients with intermittent BBB, exercise scintigraphic results were only detailed in 4: 2 were normal, 1 had normal coronary arteries and no clinical problem other than intermittent BBB, and 1 had paroxysmal atrial fibrillation but did not undergo coronary angiography. Scintigraphy was equivocal in 1 patient who also did not have coronary angiography. A single patient with a positive result had 80% left anterior descending stenosis. Significantly, in view of our results, no mention was made as to whether those patients with intermittent BBB had an episode of BBB during their exercise tests, suggesting that they did not.

The scant reports specifically dealing with exercise BBB are less comprehensive. Goodfriend et al[4] described a man who had right BBB and left-axis deviation with exercise, but also with anxiety and amyl nitrite inhalation. He died suddenly. Autopsy revealed 3-vessel CAD, but no lesions >50%. There was intimal proliferation in the arteries of the atrioventricular node and His bundle and atrioventricular nodal fibrosis. On this basis, but without scintigraphy, the investigators suggested episodic ischemia as a cause for this otherwise apparently rate-related BBB.

A 30-year-old athlete with exercise BBB had also previously displayed intermittent left BBB that was felt to be rate-dependent, occurring at 78 beats/min with postural changes and minor activity and 85 beats/min at rest during right atrial pacing.[5] He had a normal angiogram and only developed exercise BBB at 180 beats/min. The results were interpreted as suggesting autonomic influences on intraventricular conduction rather than ischemia as the cause of BBB.

Four patients with severe CAD had transient left posterior hemiblock, rather than complete BBB, with exercise.[6] To ascertain if the hemiblock was due to new, transient ischemia or if it was rate-related, the investigators paced patients to induce tachycardia above the rate at which hemiblock appeared during exercise. When it could not be induced, they concluded that it was due to ischemia.

The only reported case of exercise BBB with simultaneous thallium perfusion imaging[7] demonstrated anteroseptal ischemia in a man with proved CAD who had left BBB during exercise, thus invoking active ischemia as a cause. The patient later had an anteroseptal infarct and permanent left BBB.

Such individual case reports and data make it difficult to ascertain patterns of cause, significance, or clinical features in exercise BBB. Sandberg[8] attempted to do so; he reported 9 patients, described from clinical data alone, without coronary angiography or scintigraphy. He divided the cohort into 2 groups. One, a generally younger group of 3 patients, had left BBB only at a high level of exercise and were felt to have no cardiac disease. The remaining 6 were generally older, developed left or right exercise BBB at rather light work loads, and were regarded as abnormal because of a cardiac history such as angina. However, of the 3 apparently normal subjects, 1 had a history of chest discomfort with stress and another had a ventricular septal defect. Moreover, of the 6 patients regarded as having heart disease on history alone, only 4 had angina pectoris and 2 had had rheumatic fever without subsequent heart disease. Thus, a classification of exercise BBB from these data is flawed.

Clinical and electrocardiographic characteristics: Our data do not suggest distinct age stratification in exercise BBB. A large proportion had a known, or highly likely, pretest diagnosis of CAD: 6 had had myocardial infarcts and 3 angina. The majority of patients had an ECG abnormality before exercise. Only 2 had normal baseline electrocardiograms; 11 had a baseline IVCD or incomplete BBB. The type of exercise BBB was related to the baseline electrocardiogram. Thus, the 3 patients with incomplete right BBB had complete right BBB and the patient with incomplete left BBB had complete left BBB. Of the 7 patients with nonspecific IVCD, 5 had left BBB.

The heart rates at onset and offset of exercise BBB are interesting, particularly in view of the common conception that "rate-related" BBB is often benign. Of the 13 patients in whom BBB remitted after exercise, in 9 the onset and offset rates were within 8 beats/min. Of these 9, 2 had reversible thallium perfusion defects, 4 CAD, 1 almost certainly coronary spasm, and 2 primary myocardial disease. In 4 patients, offset rates were at least 28 beats/min lower than onset rates. Two of these had CAD (1 with old infarct and another with angiographic 3-vessel CAD), 1 had ventricular arrhythmias without other evidence of heart disease, and 1 was normal. The 3 patients in whom exercise BBB persisted all had CAD, documented by angiography in 2 and prior myocardial infarction in 1. Thus, rate-related exercise BBB was associated with an appreciable incidence of CAD or myocardial abnormalities. Conversely, in the 4 patients with discordant onset and offset rates, in whom ischemia rather than rate would

Tachycardia-related BBB is regarded as "phase 3 block" [9] with prolonged recovery and increased duration of the action potential in part of the conducting system. This may be associated with hypopolarization, which slows conduction velocity. When electrical recovery is greatly prolonged, BBB may occur at relatively slow rates, explaining exercise BBB onset at rates in the 70s in 3 of our patients. Both prolonged recovery and hypopolarization of conducting tissue can be caused by ischemia and myocardial disease. Tachycardia itself may induce or aggravate ischemia by diminishing diastolic coronary perfusion time or by exceeding the ability of damaged His-Purkinje fibers to conduct, leading to exercise BBB.

In all 13 cases of reversible exercise BBB, offset rate of BBB was equal to the onset rate or lower. This is also consistent with phase 3 block, where differences in these critical rates have been explained by prolonged duration of recovery of the affected bundle and "linking," in which retrograde activation of the affected bundle from the normally activated ventricle perpetuates this pattern of ventricular activation even when heart rate is slowed to below the rate of BBB induction, over a variable rate range.[9]

Prognosis during follow-up study is also of interest, particularly in view of the Framingham study and other data[10–12] dealing with the significance of newly acquired BBB. New left BBB was associated with a high incidence of antecedent cardiovascular abnormalities,[10] particularly hypertension, cardiomegaly, and CAD. Subsequently, such patients had a high incidence of symptoms or complications of CAD and congestive heart failure and a mortality rate from cardiovascular disease and sudden death 5 to 10 times that of age-matched control subjects without left BBB[10,11] in a 5- to 10-year follow-up, but with significant differences already apparent before 5 years. New right BBB was also associated with antecedent cardiovascular abnormalities[12]; this included hypertension in as many as 60% of the cases. As with left BBB, new right BBB was later associated with a high incidence of symptomatic CAD, heart failure, and sudden death approximately 3 times that of control subjects.[12] New right BBB was not an independent contributing factor to the increased risk of developing cardiovascular disease, but rather, a marker of increased mortality in view of its association with disorders such as hypertension.[12] In men, new left BBB contributed independently to increased risk.[10]

Our patients also had a high prevalence of pretest cardiovascular abnormalities. Of the 11 patients with exercise left BBB, 5 (45%) had an antecedent prob 3 hypertension, 1 diabetes, and 1 ventricular arrh mias. Of the 5 patients with exercise right BBB, 3 hypertension and 1 had type IV hyperlipoproteine However, over a mean 28-month follow-up study, sequent cardiovascular problems have been few. Ne of the 2 patients who died (at 7 and 32 months exercise), both with prior infarcts, had further ca vascular complications before death from unrel causes. Of the remaining 14 patients, 2 had uncon cated coronary bypass and 1 (Patient 16) had a non anterior infarct at 27 months. No other patient h subsequent morbid cardiac event.

We conclude that exercise BBB is almost alway sociated with cardiovascular disease, mostly CA often displays a "rate-related" onset and offset develops when tachycardia causes or aggravates is mia or exceeds the capacity of a damaged conduc system. It is not invariably associated with high tality or morbidity.

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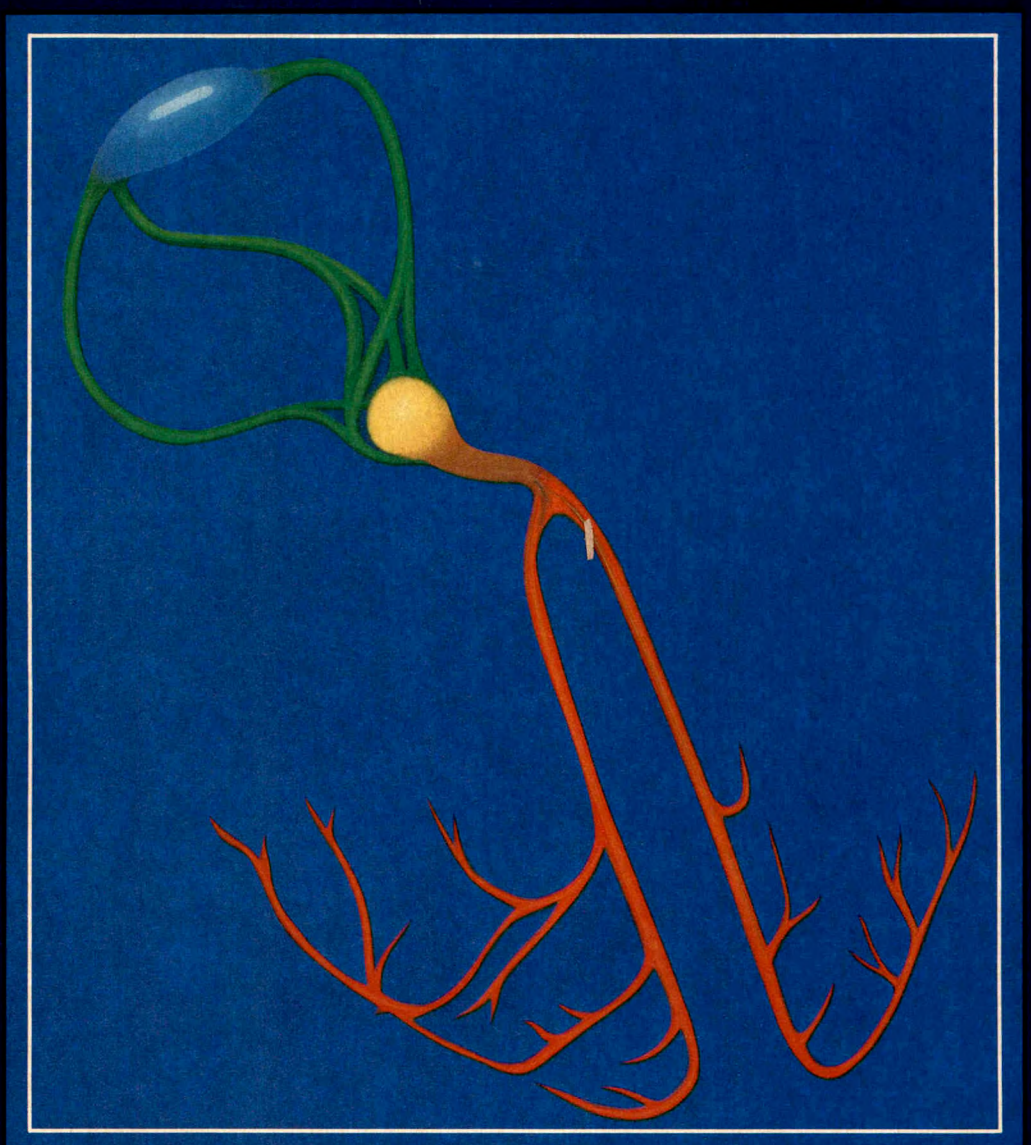

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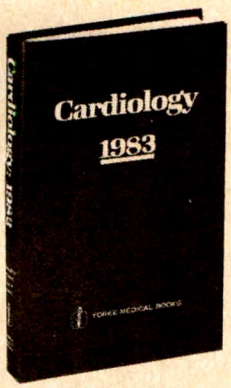

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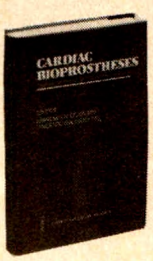

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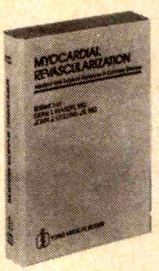

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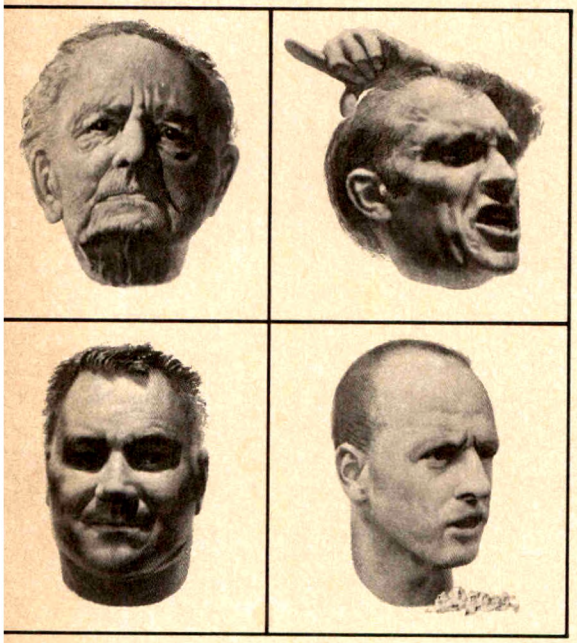

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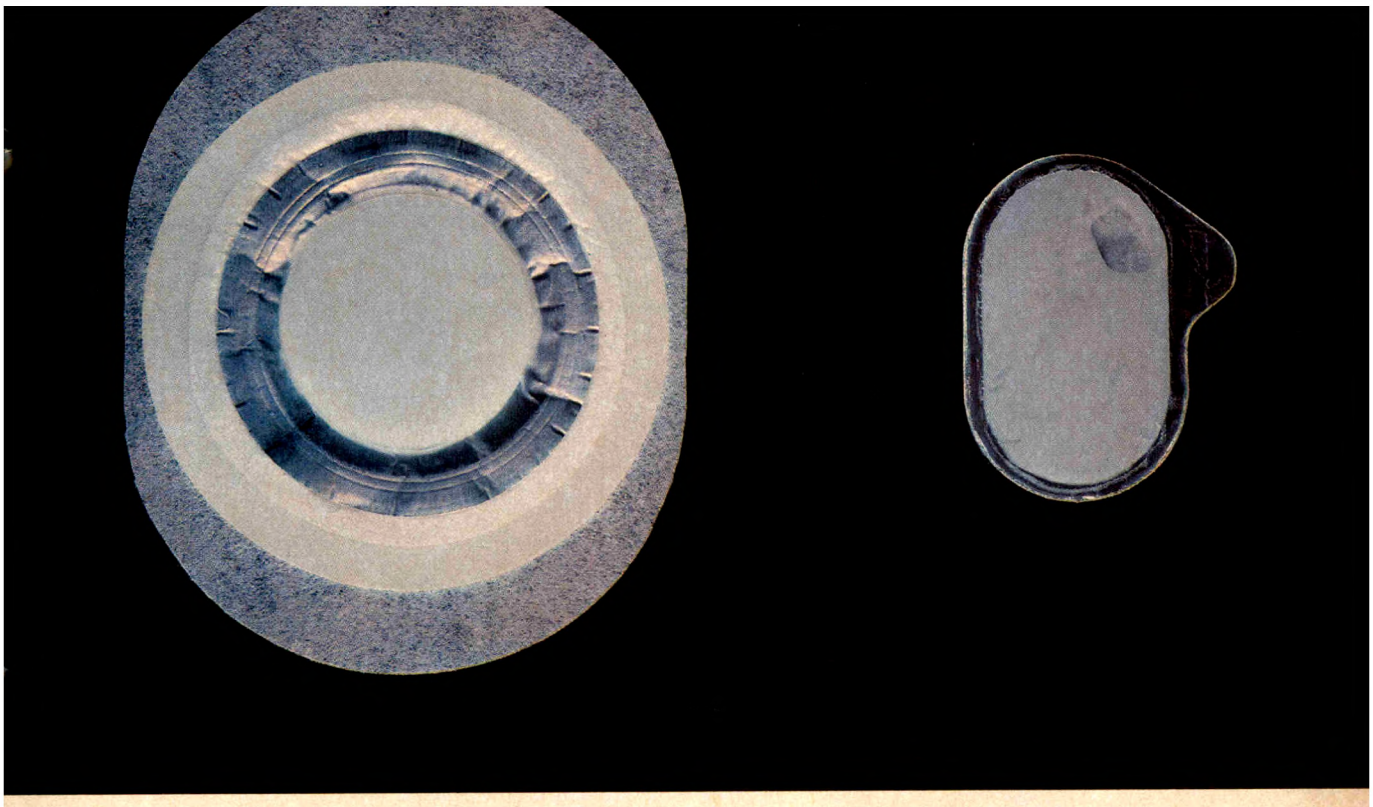

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Nitro-Dur™ (nitroglycerin) Transdermal Infusion System 10cm^2, on the left, has three times the adhesive surface area of the comparable Ciba product (5 mg). Nitro-Dur 20 cm^2 provides twice the adhesive surface area as the comparable Ciba product (10 mg). The wide adhesive strip assures good matrix-to-skin contact and helps keep the system sealed and in place. It also separates easily from the backing, for easy opening and application. By contrast, the Ciba product has minimal outside adhesion. The adhesive lies primarily on the central surface through which the drug must pass.

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Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System

The most widely prescribed transdermal nitroglycerin system.

Please see next page for a summary of prescribing information.

Nitro-Dur™
(nitroglycerin)
Transdermal Infusion System

DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing precise dosing levels of nitroglycerin. Nitro-Dur has a rated release in vivo of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies,[1] transdermal absorption of nitroglycerin from the gel-like matrix achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Therapeutic effect is achieved within 30 minutes after application of the unit, and persists about 30 minutes after removal of the unit.

INDICATIONS AND USAGE: Prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without a prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

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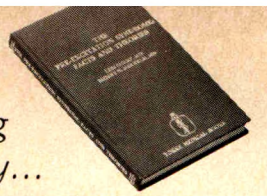

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC
Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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Pacemaker-Mediated Tachycardias: A Rapid Bedside Technique for Induction and Observation

PHILIP O. LITTLEFORD, MD, R. CHARLES CURRY, Jr., MD, KERRY M. SCHWARTZ, MD, and CARL J. PEPINE, MD

The DDD pacemaker allows sensing and pacing in both chambers and can, therefore, maintain atrioventricular synchrony. However, this pacemaker creates an additional anterograde conduction system between the atrium and ventricle and, in the presence of ventriculoatrial (VA) conduction, the possibility of pacemaker-mediated tachycardia exists. A simple bedside technique that does not require catheterization or expensive equipment was used to detect VA conduction. Just after DDD pacer implantation, an attempt was made to detect VA conduction in 31 patients. Ambulatory monitoring (Holter) was done for 24 hours after implantation and at 2 to 4 and 6 to 8 weeks after implantation to detect pacemaker-mediated tachycardia. Attempts to induce pacemaker-mediated tachycardia were made using a special programmable externa stimulator at follow-up after implantation. It wa found that (1) all the 17 patients with detectable V conduction had pacemaker-mediated tachycardi when the atrial refractory period was less than th VA conduction time, (2) pacemaker-mediate tachycardias were not inducible or detected spor taneously when atrial refractory period was equa to or greater than VA conduction time + 50 ms, (3 VA conduction was not detectable in 9 of the 1 patients at a later visit. Six of these 9 receive antiarrhythmic therapy or had developed congestiv heart failure. VA conduction has important impl cations in patients with DDD pacemakers and ca be readily evaluated at the bedside.

Since the recent introduction of a pacemaker that senses and paces in both the atrium and ventricle (DDD or universal pacemaker), pacemaker-mediated tachycardias have been observed.[1–3] A pacemaker that senses spontaneous atrial activity and paces the ventricle accordingly is analogous to an "accessory" pathway. In the presence of intact retrograde ventriculoatrial (VA) conduction, this implanted "accessory" pathway provides the potential for a reentry type circuit. Recent observations by Furman[4] and others[5,6] suggest that pacemaker-mediated tachycardias are a very common problem with DDD pacemakers. It has been proposed that manipulation of atrial sensing or the atrial refractory period of this pacemaker may control or prevent these pacemaker-mediated tachycardias.[4,5]

These suggestions generate numerous questions: Does the presence of VA conduction uniformly lead to pacemaker-mediated tachycardias? Can pacemaker-m diated tachycardia be prevented by manipulation the atrial refractory period? Can the presence of V conduction be readily detected in patients with pac makers? Are there any clinical characteristics of V conduction which relate to the presence of pac maker-mediated tachycardias? The purpose of th study was to evaluate a simple bedside technique detect and measure VA conduction in patients wi DDD pacers. When VA conduction was detected, th relation between the duration of the VA conductic time and the pacemaker atrial refractory period w examined with regard to the presence or absence pacemaker-mediated tachycardia.

Methods

Patient selection: Patients with sick sinus syndrome, hea block, or both, referred for pacemaker implantation we considered candidates for this study. From January 4, 198 to September 14, 1982, 31 patients were selected. Sixteen we males and 15 females, average age 74 years. Each patient ga informed consent and a DDD pacemaker was implanted usi standard techniques.

Procedure: At the time of implantation, an attempt w made to detect VA conduction. This was accomplished aft

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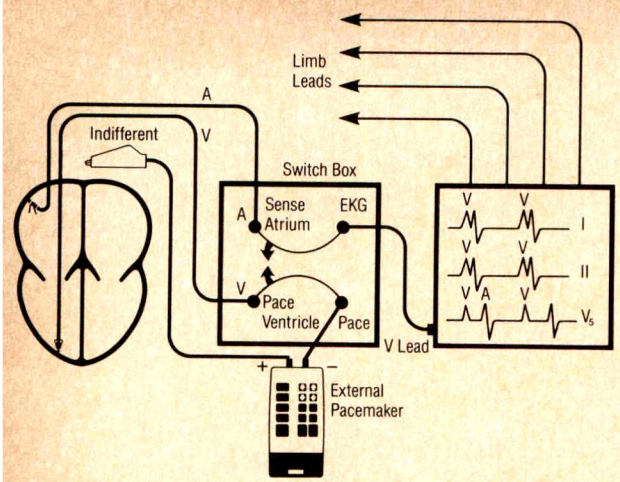


IGURE 1. Connections and switching arrangements used to detect entriculoatrial conduction during implantation. A switching box (**center**) connected to the atrial (A) and ventricular (V) leads. The other side f the switching box is connected to the cathode of a standard external acemaker (**bottom**) and to the V lead of a standard 3-channel electrocardiographic recorder. The anode of the external pacemaker is onnected to an indifferent lead applied to the skin. This arrangement lows the ventricle to be paced with recording of the atrial electroam.

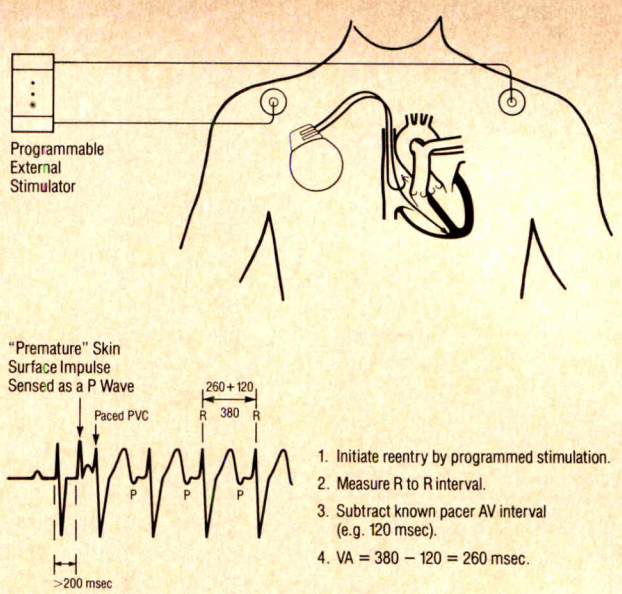


FIGURE 2. Induction of pacemaker-mediated tachycardia (PMT) by a programmed stimulator. A programmed stimulator is set to deliver an impulse to the skin 200 ms after the onset of ventricular depolarization. This impulse is sensed by the implanted DDD pacemaker atrial section as a P wave. After the programmed A-V interval, the DDD pacemaker stimulates the ventricle (paced PVC). When ventriculoatrial (VA) conduction is present, the atrium is depolarized (P), the pacemaker atrial section senses the P wave and again stimulates the ventricle, initiating PMT. VA conduction time is measured as outlined. PVC = premature ventricular contraction.

hreshold measurements, stabilization of the leads, and before he pulse generator was connected and the incision closed. When VA conduction was present, the duration was measured n milliseconds and termed *VA conduction time.* The VA onduction time was taken as the interval from the onset of he pacing artifact to the initial fast deflection of the atrial lectrogram. The implanted atrial and ventricular leads were ised for sensing and pacing, respectively, with a ventricular acing rate arbitrarily set at 90 beats/min. A special switching ox (Fig. 1) was used and allowed measurement of atrioventricular conduction as well. Depending on the type of pulse enerator used* the atrial refractory period (time of atrial onsensing after a sensed or paced ventricular event) was rogrammed to its shortest duration.

Twenty-four-hour electrocardiographic (ECG) recordings Holter) were made to determine the presence or absence of pacemaker-mediated tachycardia. After these recordings, VA conduction was detected, the pulse generator was reprogrammed so that the atrial refractory period was no less han 50 ms longer than the measured VA conduction time. his value was chosen in an attempt to select the shortest nterval that would compensate for variations in VA conuction. At the time of implantation, the actual programmed alues ranged from 50 to 100 ms. Another Holter ECG recording was then done in an attempt to detect a pacemakerediated tachycardia. The patient was then discharged. ostoperative visits were made between the second and fourth eek and again between the sixth and eighth week. At these sits, using a specially designed external programmable pulse enerator, attempts were made to initiate pacemaker-mediated tachycardia.

Technique used to attempt to initiate pacemaker-ediated tachycardia (Fig. 2): Two skin electrodes were tached, 1 to the right and the other to the left shoulder. An external pulse generator (Cordis Orthocor 1A overdriver, model 230A) was then attached to the electrodes and programmed to discharge an impulse at an interval ≥200 ms after the onset of ventricular depolarization detected from the electrocardiogram. This programmed impulse was delivered to the skin electrode and sensed by the atrial section of the pulse generator as an "atrial event." After the programmed atrioventricular interval, the pulse generator then paced the ventricle. When VA conduction was present, the atrium was activated in retrograde fashion. The atrial section of the pacemaker sensed the retrograde P wave and again paced the ventricle, initiating the pacemaker-mediated tachycardia. From ECG recordings made at fast paper speed, the paced R-R interval was measured. The pacemaker atrioventricular delay was subtracted to yield VA conduction time (Fig. 2). This was done with the pacemakers programed to upper rate limits (≥160 beats/min). The procedure was repeated 3 to 6 times and the VA conduction times recorded. The mean value was calculated.

Results

Of the 31 patients tested, in whom DDD pacemakers were implanted, VA conduction was detected in 17. Pertinent clinical and electrophysiologic data from these 17 patients are summarized in Table I. In 15, VA conduction was detected at implantation and in 2 when pacemaker-mediated tachycardia developed, within 2 hours of implantation (Patients RH and EM).

Of the 17 patients who had VA conduction detected in the hospital, VA conduction persisted in 12 at the first postoperative visit. In each case, the atrial refractory period of the pacer was ≥50 ms more than the VA con-

* Cordis Sequicor and Gemini units have programmable atrial refractory periods, whereas Medtronics Versatrax I and Telectronics ıtima have fixed atrial refractory periods of 155 and 200 ms, rectively.

TABLE I Summary of Pertinent Clinical and Electrophysiologic Data in Patients With Ventriculoatrial Conduction Detected at or Shortly After Implant

Patient	Age (yr) & Sex	Diagnosis	AV (ms)	VAop (ms)	VA_2 (ms)	VA_3 (ms)	Comment
RC	72M	SSS/1°HB	220	240	Died		
ES	88F	Int/3°HB	250	300	275	Explanted	Infection
ES	83M	SSS/Int 3°HB	260	220	235	230	
WE	75M	Int/3°HB	380	340	365	0	CHF
PB	74M	SSS	280	200	0	Died	CHF
RB	74F	SSS	240	260	0	0	A fib
EC	78F	SSS/A fib	160	185	200	200	
EB	77F	SSS/1°HB	290	235	235	225	
ET	75M	SSS	230	240	230	0	Nadolol
HS	69M	SSS/Int 3°HB	240	240	230	0	CHF
PD	82F	SSS/PAT	200	295	330	0	Procainamide
JO	90F	Int 3°HB	360	250	255	0	
LB	65F	SSS/1°HB	410	500	0	0	
RH	68M	SSS	230	0*(150–2 hours later)	150	0	CHF
EM	68M	SSS/1°HB	250	0*(185–2 hours later)	0	0	
HK†	67M	SSS	320	250	245 260	235 265	Dual pathway
JB†	76M	SSS	120	220	240 350	350	Dual pathway

* Absent at implant—present within 2 hours.
† "Dual pathways."
A fib = atrial fibrillation; AV = atrioventricular conduction time; CHF = congestive heart failure; Int = intermittent; SSS = sick sinus syndrom
VA = ventriculoatrial conduction time in milliseconds; VA_2 and VA_3 = VA measured at the first and second postoperative visits, respectively; VAo
= ventriculoatrial conduction time measured at operative implantation; 1° and 3° HB = first- and third-degree heart block.

duction time. In these 12 patients, VA conduction time at implantation was closely correlated with VA conduction time recorded at the first postoperative visit (Fig. 3). One patient died before the first visit (RC). In the other 4 patients, VA conduction was not detected at the first postoperative visit. One of these 4 patients (PB) was in congestive heart failure at the first visit; another (RB) had atrial fibrillation. One patient (LB) had very prolonged VA conduction measured at the time of implantation and in 1 (EM), no explanation wa found for the absence of VA conduction.

Of the 12 patients who had VA conduction detecte at the first postoperative visit, it was not detectable a the second postoperative visit in 7. Another (ES) ha the pacemaker removed because of infection. Thre patients (WE, HS, and RH) who now had congestiv heart failure had no VA conduction. Two patients (E'

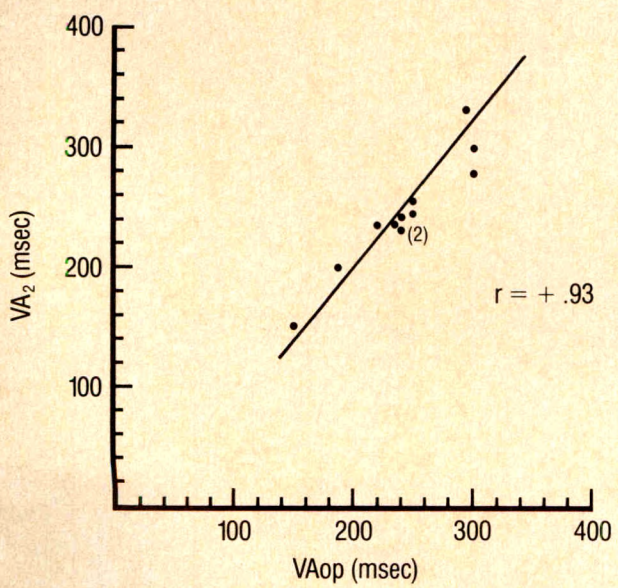


FIGURE 3. Relation of ventriculoatrial (VA) conduction time at implantation (VAop) to that at the first postoperative visit (VA_2) in the 12 patients who had detectable VA conduction at the first visit. When VA conduction persisted, its duration was relatively constant.

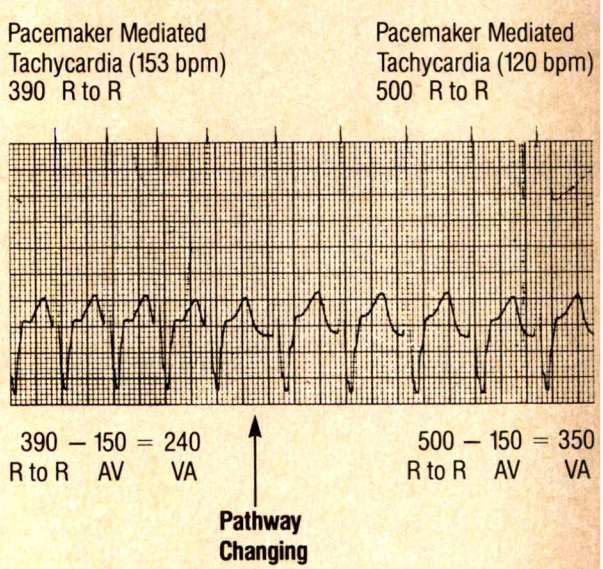


FIGURE 4. Changing pathways in pacemaker-mediated tachyca dias—example from 1 patient (JB) with pacemaker-mediated tach cardia occurring at 2 different rates. The A-V interval was fixed by th pacer and there was no evidence for atrial tachycardia, suggesting a ternate or dual pathways to explain the variation in ventriculoatrial (V conduction time. The upper rate limit in this patient was programme at 180 beats/min.

nd PD) were receiving antiarrhythmic therapy (pro-
ainamide and nadolol). In 1 patient (JO) there was no
pparent explanation for the absence of VA conduction.
nother patient (PB) died before the second visit.

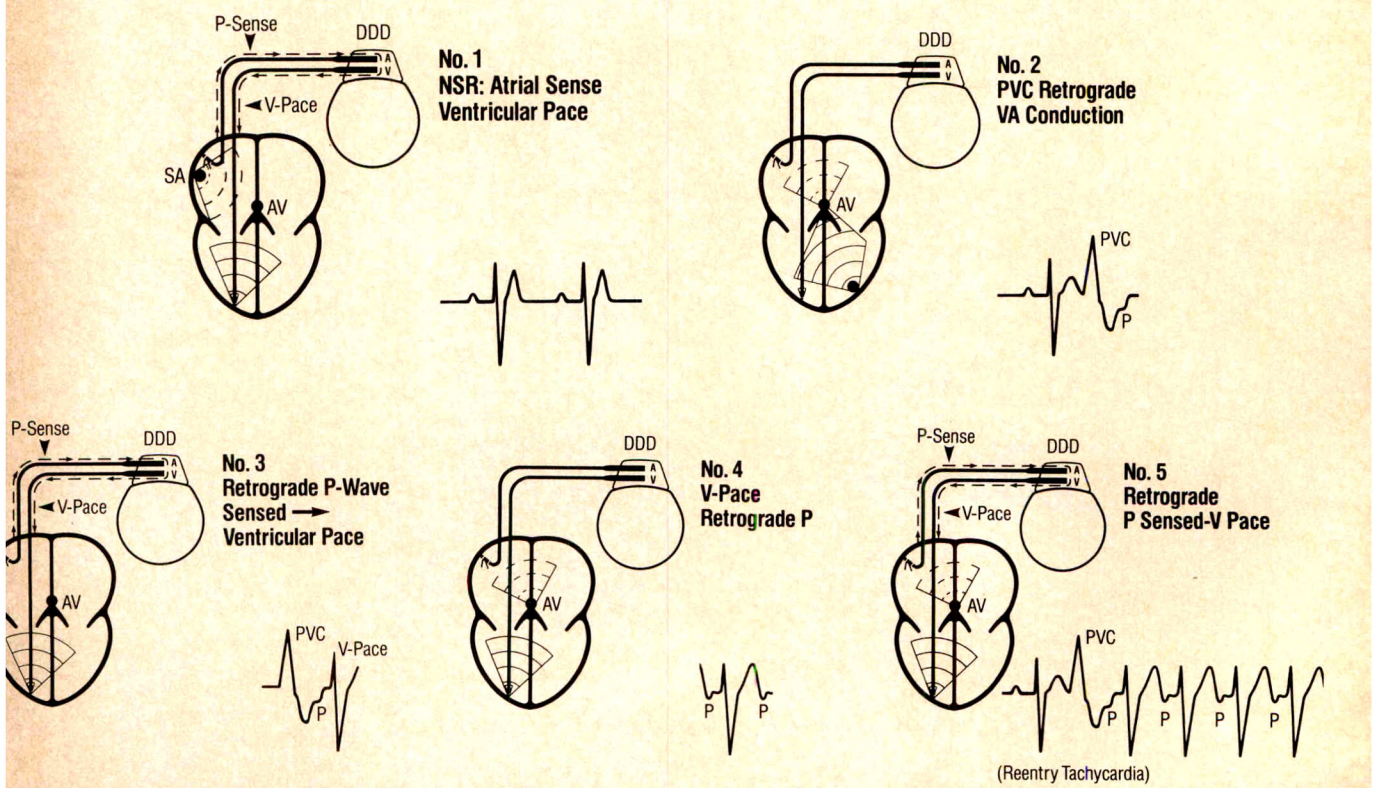
In the 17 cases with VA conduction, pacemaker-
ediated tachycardia occurred after a spontaneously
ccurring premature ventricular contraction in each
atient. In 15 of these 17 patients, the pacemaker-
ediated tachycardia rates were constant (±2%) for any
iven patient. Two patients (HK and JB) had pace-
aker-mediated tachycardia at 2 different rates. This
ggested the possibility of alternate or dual VA path-
ays, since the A-V interval would be fixed by the pacer
Table I, Fig. 4). Long multilead rhythm strips did not
ggest sinus tachycardia or atrial flutter. In both cases,
hen the pacemaker atrial refractory period was pro-
rammed to ≥50 ms more than the longest VA con-
uction time, pacemaker-mediated tachycardia could
ot be induced or seen by Holter ECG recordings.

Two patients (RH and EM) did not have VA con-
uction detected at implant; however, within 2 hours
f the procedure they had pacemaker-mediated
chycardia. At that time, relatively short VA conduc-
on times were found (150 and 185 ms, respectively).
t follow-up, when VA conduction was no longer de-
ctable, we could not initiate pacemaker-mediated
chycardia in either of these patients. One had devel-
ped congestive heart failure, but in the other there was
o apparent explanation for disappearance of VA con-
uction.

Discussion

Pacemaker-mediated tachycardias appear to be relatively common occurrences associated with DDD pacemaker implantation.[4–6] The most frequent initiating event appears to be a premature ventricular contraction. A DDD pacemaker can sense and pace in both the atrium and ventricle. Should the patient have a premature ventricular contraction and intact VA conduction, the potential to depolarize the atria in a retrograde fashion is present. If the pacemaker's atrial sensing is set so that the atrial refractory period is exceeded, the retrograde P wave will be sensed by the pacer and the ventricle will be paced after the appropriate delay. This sequence yields another retrograde P wave and the cycle continues (Fig. 5).

In 31 patients, we assessed VA conduction at implantation and twice after implantation using a simple bedside technique. Seventeen patients had detectable VA conduction and all subsequently had pacemaker-mediated tachycardia. Holter ECG recordings in these 17 patients revealed that a spontaneous premature beat triggered each tachycardia episode. In theory, any asynchronous beat could give rise to pacemaker-mediated tachycardia. For example, this could occur when the pacemaker is made asynchronous by brief application of a magnet or programmer. Another potential triggering event results when skeletal muscle signals are sensed by the atrial chamber, triggering the pacemaker to stimulate the ventricle.[3]



URE 5. Sequence that initiates pacemaker-mediated tachycardia by a premature ventricular contraction (PVC). AV = atrioventricular node; R = normal sinus rhythm; P-Sense = P wave sensed by atrial section of pacer; SA = sinoatrial node; VA = ventriculoatrial; V-Pace = ventricular ivation sensed by ventricular section of pacer.

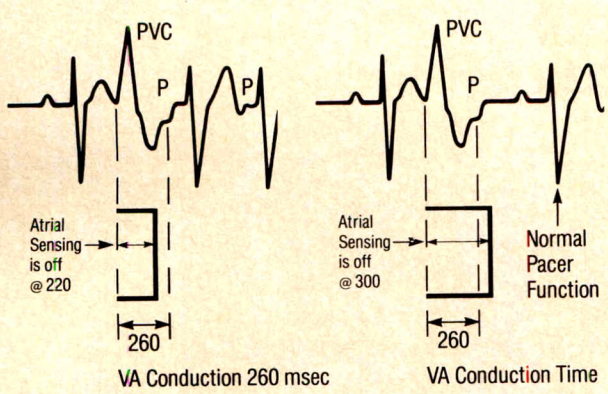


FIGURE 6. Importance of the relation of the atrial refractory period to ventriculoatrial (VA) conduction time in preventing pacemaker-mediated tachycardias. When VA conduction time is 260 ms (**left**) and atrial refractory period is 220 ms, the P wave resulting from conduction of the PVC to the atrium is sensed, resulting in pacemaker-mediated tachycardia. When the atrial refractory period is lengthened to 300 ms (**right**), the P wave is not sensed and normal pacemaker function results.

A potential problem with the method used to determine VA conduction time in outpatients is that it depends on the programmed upper rate limit of the pacemaker. Thus, if VA conduction time plus the programmed A-V interval time is less than the minimum allowable R-R interval because of upper rate limit constraints, the A-V interval will be artifactually prolonged by the pacemaker. In this case, subtracting the programmed A-V interval from the R-R interval gives an erroneous value for VA conduction time. This limitation was avoided by programming the pacemaker to high upper rate limits (≥160/ms).

The relationship of the pacemaker atrial (nonsensing) refractory period to the VA conduction time appears to be of central importance in controlling pacemaker-mediated tachycardia. This is illustrated in Figure 6. In this case, VA conduction time is 260 ms. When the atrial refractory period (atrial nonsensing) is 220 ms, the P wave can be sensed and the pacemaker-mediated tachycardia initiated. When the atrial refractory period is 300 ms, the retrograde P is not sensed and normal pacemaker function resumes after the premature beat. Since the pacemaker's atrial nonsensing or refractory period is constant, the constancy of VA conduction is most important. If the duration of VA conduction varied markedly with time, then control by reprogramming the atrial refractory period of the pacemaker would not be expected to influence the pacemaker-related arrhythmias in a predictable manner. In the group of patients we evaluated, VA conduction, when present, did not appear to vary significantly over time (Fig. 3). VA conduction time at the time of implantation was closely correlated with VA conduction time at the first postoperative visit ($r = 0.93$) in this subset of patients. Although VA conduction did not appear to vary significantly in this subset, procainamide, nadolol, and congestive heart failure were associated with absence of detectable VA conduction in some patients.

In 2 patients, we did not detect VA conduction at the time of the actual operative implantation procedure. Within several hours, they both developed pacemaker-mediated tachycardias with relatively short VA conduction times. Thus, the inability to detect VA conduction at the time of operative implantation may not necessarily mean that VA conduction will be absent at a later period.

In the first generation of DDD pacemakers, only 1 of the 3 frequently used pacemakers can vary the atrial refractory period. From our results, this programmable parameter is important for control of pacemaker-mediated tachycardia without addition of drugs to influence VA conduction or premature ventricular beats. From a practical point of view, it would appear relatively safe to set the atrial refractory period of the DDD pacemaker from 300 to 350 ms. This value includes settings that prevented tachycardia in all but 2 patients (WE and JB) in our series. If we assume A-V intervals of 125 to 150 ms, the shortest possible R-R interval would be (125 + 300) or 425 ms and the fastest heart rate would be 141 beats/min. At 150 ms, with an atrial refractory period of 350 ms, the shortest R-R interval would be 500 ms and the fastest heart rate 120 beats/min. This practice would limit the tachycardia rate to 120 or 140 beats/min.

In conclusion, VA conduction was detected frequently after DDD pacemaker insertion. Detection of VA conduction was uniformly associated with pacemaker-mediated tachycardia, and pacemaker-mediated tachycardia was prevented by manipulation of the atrial refractory period. When present over a period of time, VA conduction tends to be remarkably constant in duration, but may disappear in the setting of either congestive heart failure or antiarrhythmic therapy. An atrial refractory period of 300 to 350 ms should control pacemaker-mediated tachycardia in most cases.

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Intermittent Preexcitation in the Wolff-Parkinson-White Syndrome

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Intermittent loss of the delta wave in the Wolff-Parkinson-White (WPW) syndrome may result from precarious conduction over the accessory pathway and, as such, would predict a benign prognosis in the event of the occurrence of atrial fibrillation (AF). We evaluated 52 consecutive patients referred for the assessment of the WPW syndrome and determined the prevalence of intermittent preexcitation using review of serial electrocardiograms, ambulatory monitoring, and treadmill testing. All patients subsequently had electrophysiologic testing using standard techniques to determine the properties of the accessory pathway. Of the 52 patients, 26 (50%) were found to have intermittent preexcitation as defined by loss of the delta wave with concomitant prolongation of the P-R interval on at least 1 occasion. These patients had longer effective refractory periods of the accessory pathway (356 ± 114 versus 295 ± 29 ms, mean ± standard deviation, $p < 0.05$) and longer shortest cycle lengths maintaining 1:1 anterograde conduction (426 ± 171 versus 291 ± 63 ms, $p < 0.02$) than their counterparts with constant preexcitation. During AF, 15% of patients with intermittent preexcitation had shortest R-R intervals between preexcited beats <250 ms, versus 50% of patients with constant preexcitation ($p < 0.01$). These data support the hypothesis that intermittent preexcitation suggests a benign prognosis in the event of AF. A careful search for intermittent preexcitation may yield important prognostic information in asymptomatic subjects and obviate further investigation.

The abnormal QRS complex in the Wolff-Parkinson-White (WPW) syndrome generally results from fusion between depolarization occurring via conduction over the normal atrioventricular conduction system and that occurring over an accessory atrioventricular (Kent) pathway with the delta wave resulting from preexcitation of the ventricle via the accessory pathway.[1,2] Intermittent preexcitation or intermittent loss of the delta wave has been observed[2–5] and generally attributed to a "low margin of safety" [6] of conduction over the accessory pathway, although other mechanisms have been proposed.[6–10]

Sudden death in the WPW syndrome can result from the occurrence of atrial fibrillation (AF) with a very rapid ventricular response due to conduction over an accessory pathway.[11] The purpose of our investigation was to estimate the prevalence of intermittent preexcitation in our referral population of patients with the WPW syndrome and to test the hypothesis that intermittent preexcitation correlates with a moderate ventricular response during AF.

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Methods

The study group consisted of 52 consecutive patients referred to the Clinical Electrophysiology Laboratory at University Hospital between March 1980 and March 1982 for management of the WPW syndrome. Thirty-five patients had documented tachycardia (AF or reciprocating tachycardia), and the remaining 17 were asymptomatic, having been referred for evaluation as part of an ongoing natural history study of the WPW syndrome at our institution.

Intermittent preexcitation, defined as loss of the delta wave with concomitant prolongation of the P-R interval, was sought prospectively in all patients. Utilizing electrocardiograms (ECGs) forwarded by referring physicians and those recorded at University Hospital, at least 3 separate 12-lead ECGs were available for each patient. ECGs recorded during known antiarrhythmic medication were excluded. A 24-hour ambulatory ECG was obtained in all patients in the absence of antiarrhythmic medication. For this recording, the single lead displaying the most prominent delta wave was sought empirically. The tapes were scanned by a technician specifically instructed to focus on the presence or absence of the delta wave. All patients underwent a graded treadmill exercise test (Bruce) in the absence of medication. Standard 12-lead ECGs were recorded during each phase of this test.

TABLE I Clinical Profile

	Constant Preexcitation	Intermittent Preexciation
Age (mean ± SD [yr])	37 ± 13	40 ± 15
Male:female	19:7	13:13
Asymptomatic (%)	31	35
Multiple AP (%)	8	8
Septal versus free wall AP* (%)	46	54
Organic heart lesion (%)	11	11

* Only 4 patients had a right free wall accessory pathway, and 3 of these were in the intermittent group.

Data were compared using Student's *t* test; none were significant.

AP = accessory pathway; SD = standard deviation.

Patients were classified as having intermittent preexcitation if loss of the delta wave was observed on at least 1 occasion with the aforementioned investigations. All patients then underwent invasive electrophysiologic studies in the nonsedated, postabsorptive state in the absence of antiarrhythmic medication using methods previously described.[12,13] Informed consent was obtained before all studies. Specifically, incremental atrial pacing at 1 or more sites was performed to assess conduction over the accessory pathway, and atrial extrastimulus testing at 2 or more cycle lengths was done to determine the refractory period of the accessory pathway. The induction of AF was attempted in each patient if this arrhythmia did not occur spontaneously during the study.

Results

Determination of intermittent preexcitation: Twenty-six patients (50%) were found to have intermittent preexcitation. There was no difference in age, sex, symptomatic status, or location of accessory pathways in patients with and without this phenomenon (Table I). Eleven patients in the total study population were documented to have spontaneous AF, of whom 8 were in the constant preexcitation group.

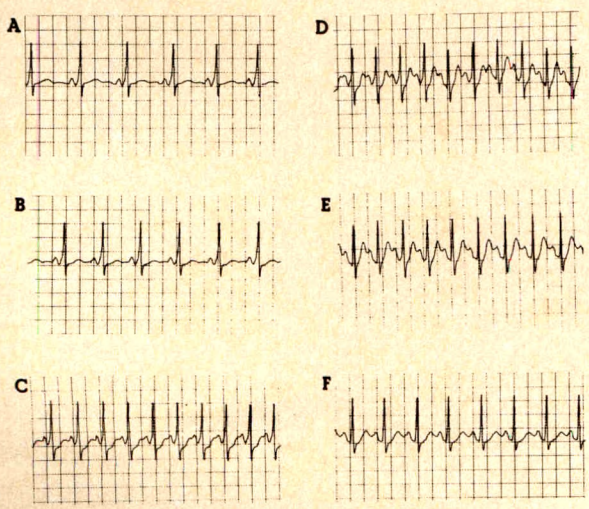

FIGURE 1. Loss of preexcitation occurring suddenly during the recovery phase of exercise testing. Lead II is shown. Preexcitation is present at rest (**A**) and during stress (**B and C**). Sporadic loss of the delta wave is seen in the early postexercise period (**D and E**). Normalization is constant in the later postexercise period (**F**), and this was observed in the other leads as well. The heart rate in **F** is slower than in **C**, yet the latter remains preexcited while the former is normalized.

Serial ECGs showed intermittent preexcitation in 14 patients. Nine patients had separate ECGs showing entirely normal or entirely preexcited QRS, while 2 patients showed sudden loss of preexcitation in the same tracing. Three patients exhibited both of the above patterns.

Seventeen patients lost preexcitation at the time of exercise testing. Normalization of the QRS occurred during exercise in 7 patients and during recovery in 1 patient (Fig. 1), and occurred sporadically in a single patient. Eight patients had a normal QRS at the onset of exercise, and 2 of the latter patients developed preexcited QRS during stress. Many patients appeared to lose preexcitation in 1 or more leads, while preexcitation was clearly persistent in other leads recorded simultaneously or nearly so (Fig. 2). The latter patients were not considered to have lost preexcitation. Only normalization of the QRS seen in all available leads and accompanied by P-R interval prolongation was considered to represent loss of preexcitation.

Twenty-one patients lost preexcitation during ambulatory monitoring (Fig. 3). Loss of preexcitation ap-

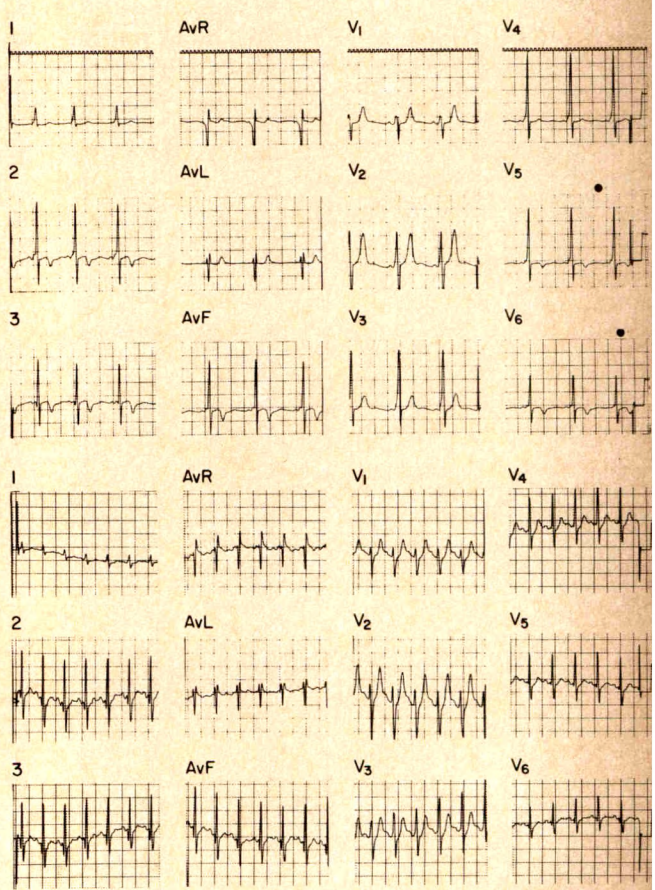

FIGURE 2. Apparent loss of the delta wave at peak stress. A delta wave is clearly present at rest (**top**). During maximum stress (**bottom**), the delta wave has disappeared from many leads, notably lead II (**2**). The normalization was accompanied by repolarization changes and an increase in amplitude of the P wave. A subtle delta wave is still present in lead V_3, indicating continued preexcitation and emphasizing the importance of examining multiple leads.

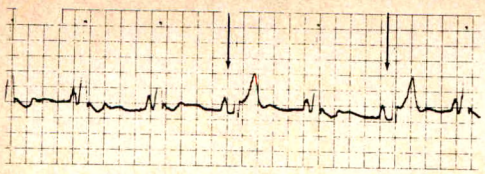

FIGURE 3. Sporadic, sudden loss of the delta wave (**arrows**) recorded during ambulatory monitoring. Loss of the delta wave is sudden and not accompanied by a change in heart rate. Repolarization changes accompany the loss of the delta wave.

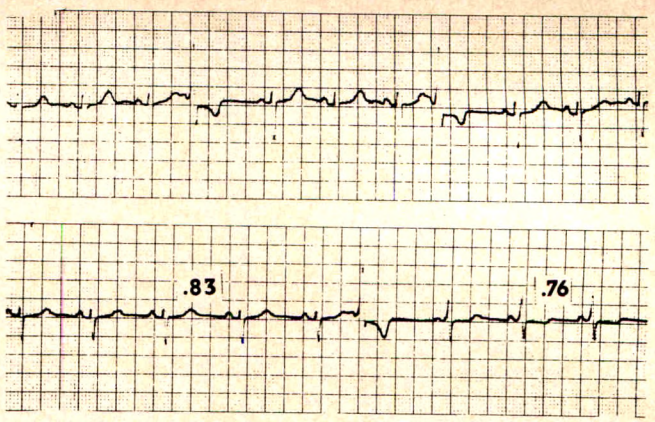

FIGURE 4. Sudden appearance of preexcitation after premature atrial contraction (PAC) (**lower panel**) recorded during ambulatory monitoring. The heart rate is slightly faster after the appearance of the delta wave, but no consistent relationship was observed in this record. Numbers represent R-R intervals in seconds.

peared related to a critical heart rate in 2 patients and was sporadic in 12 patients (Fig. 4). Seven patients had only a normal QRS during ambulatory monitoring.

Electrophysiologic testing: As a group, patients with intermittent preexcitation demonstrated a longer anterograde effective refractory period of the accessory pathway at comparable cycle lengths and a longer minimum cycle length, maintaining 1:1 conduction over the accessory pathway (Fig. 5). Thirteen of 26 patients with constant preexcitation had very rapid rates due to anomalous conduction during AF (shortest R-R interval between preexcited beats, 250 ms), versus 4 of 26 with intermittent preexcitation ($p < 0.01$, Fig. 6). The use of 250 ms as a cut-off was based on a previous study of ventricular fibrillation in the WPW syndrome[11] in which all WPW patients with this complication had shortest R-R intervals <250 ms during AF induced in the laboratory.

Resting P-A, A-H, and H-V intervals were similar in the 2 groups. Six patients with intermittent preexcitation had no retrograde conduction over the accessory pathway, versus 5 patients with constant preexcitation. The minimum cycle length maintaining 1:1 retrograde conduction over the accessory pathway was 305 ± 105 ms (mean ± standard deviation) for patients with intermittent preexcitation, versus 300 ± 60 ms for patients with constant preexcitation.

Discussion

Intermittent loss of the delta wave has been consistently observed by investigators of the WPW syndrome, but the mechanism underlying this phenomenon is not known.[2,9,14–17] Our data demonstrate that patients with

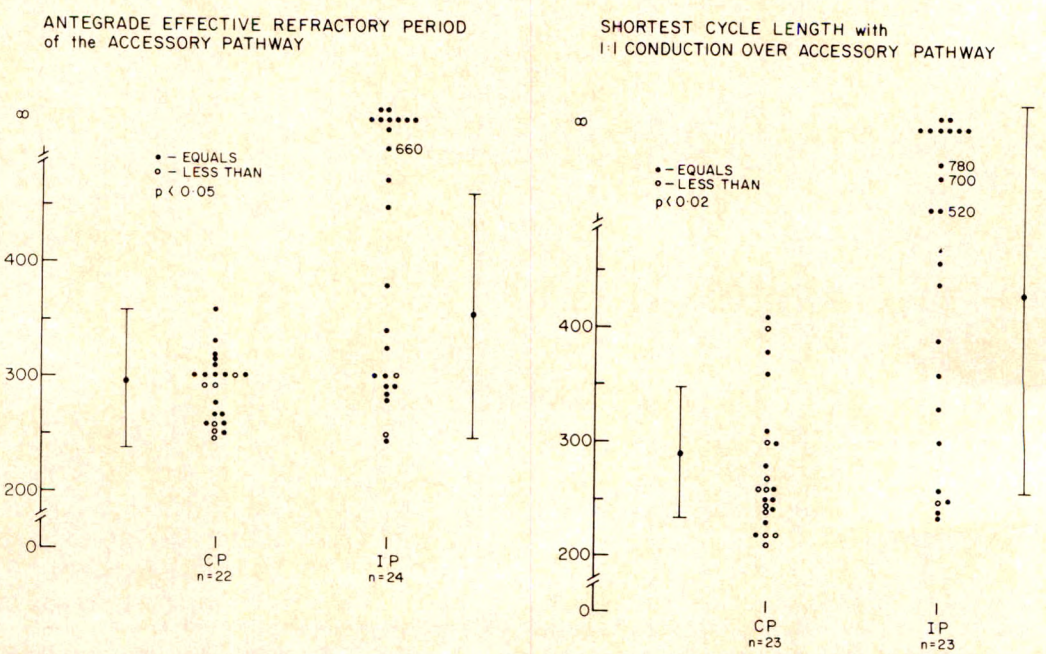

FIGURE 5. Anterograde effective refractory period (cycle length 600 or 700 ms) of the accessory pathway (**left panel**) and shortest cycle length with 1:1 conduction over the accessory pathway (**right panel**). Comparison between patients with and without intermittent preexcitation is shown. CP = constant preexcitation; IP = intermittent preexcitation; ∞ = no preexcitation at any paced cycle length. (The means do not include values designated as ∞, and consequently the actual significance is probably underestimated.)

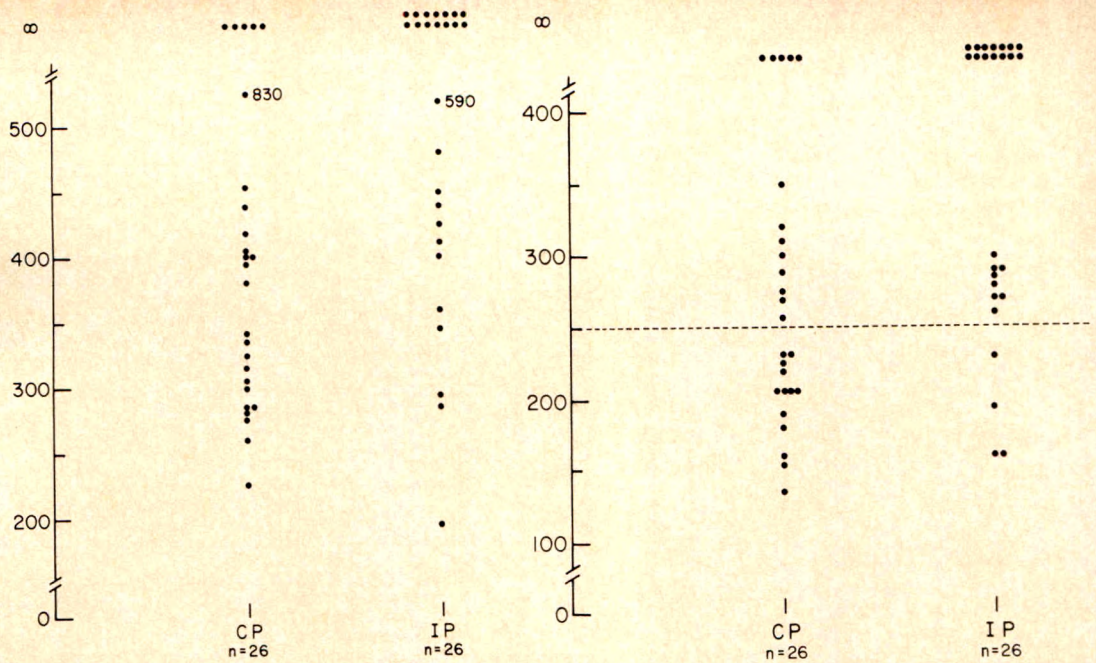

FIGURE 6. The average R-R interval (**left panel**) and shortest R-R interval between preexcited beats (**right panel**) during atrial fibrillation. Comparison of patients with and without intermittent preexcitation is shown. Fifteen percent of patients with intermittent preexcitation (IP) had a shortest R-R interval between preexcited beats <250 ms versus that in 50% of patients with constant preexcitation (CP) ($p < 0.01$). ∞ = no preexcited complexes during atrial fibrillation. (The means are not calculated because most patients with intermittent preexcitation had values designated as ∞.)

intermittent preexcitation have a longer refractory period of the accessory pathway and poorer conduction over the pathway than patients with constant preexcitation. In fact, 14 of 26 patients with intermittent preexcitation had no preexcited QRS during AF (Fig. 6). This supports the hypothesis that intermittent preexcitation is a manifestation of an accessory pathway with "precarious" conduction. This finding may have significant clinical relevance in the management of asymptomatic or minimally symptomatic patients with the WPW syndrome. Sudden death may occur in these patients and is usually related to AF occurring in the setting of an accessory pathway with a short anterograde refractory period.[11] The finding of intermittent preexcitation would suggest that the heart rate during AF would be moderate and would not degenerate into ventricular fibrillation. Conversely, the finding of constant preexcitation was not helpful.

The prevalence of intermittent preexcitation as determined largely by serial follow-up of ECGs or ambulatory monitoring has ranged from 25 to 76%,[2,9,14–18] whereas normalization of the QRS with exercise occurs less frequently, in 3 to 29% of patients.[9] Strasberg et al[19] observed sudden QRS normalization and concomitant P-R prolongation during exercise in 4 of 36 WPW patients and further observed that these patients had accessory pathways with relatively long anterograde refractory periods. This group also emphasized the frequent occurrence of QRS normalization without P-R prolongation and pointed out that the latter was related to "enhanced atrioventricular nodal conduction" rather than true loss of preexcitation. In our series, intermittent preexcitation was observed in 27% of patients by review of serial ECGs, in 46% by use of serial ECGs and ambulatory monitoring, and in 50% using serial ECGs, ambulatory monitoring, and treadmill testing. Loss of preexcitation was generally sporadic and not related to a critical heart rate, an observation also made by others.[2,18,20] It is possible that more prolonged observation periods would have increased the observed prevalence of intermittent loss of the delta wave.

Four patients with intermittent preexcitation were observed to have rapid ventricular rates during AF (shortest R-R interval between preexcited beats <250 ms) and appear to contradict the general findings. Although the mechanism for loss of the delta wave in these patients must remain speculative, the key issue is whether apparent normalization of the QRS represented total loss of preexcitation. Ohnell[2] defined "pseudonormalization" as apparent loss of the delta wave with subtle preexcitation still present. Pseudonormalization occurred gradually, whereas true normalization was abrupt and was usually accompanied by repolarization changes. In 3 of our patients in this group loss of a subtle delta wave occurred during ambulatory monitoring of a single lead. It is possible that a single lead may show apparent normalization when this is not verified by inspection of other leads[15] (Fig. 2). One of the foregoing patients had 2 accessory pathways (septal left lateral), and it is possible that the interplay of multiple accessory pathways could cancel the delta wave in some leads.[6] The fourth patient in this group had loss of a small delta wave with P-R prolongation at maximal exercise. The difficulties of interpretation of preexcitation during stress testing have been emphasized.[5] Changes in body position as well as atrial and ventric

ular repolarization could result in apparent loss of the delta wave, especially when the latter is subtle. Finally, one cannot rule out the possibility of a striking dependence of accessory pathway conduction on sympathetic tone in some patients,[21,22] resulting in presence or absence of anomalous conduction. We feel that the latter 4 patients may not have truly lost preexcitation, but that interpretive difficulties were created by a subtle delta wave viewed only in a single lead or during maximal exercise. In support of this, no patient exhibiting sudden (Mobitz 2) normalization of a prominent delta wave was found to have rapid AF due to anomalous conduction.

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Malignant Hypertension in Women Aged 15 to 44 Years and Its Relation to Cigarette Smoking and Oral Contraceptives

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To study the factors associated with malignant hypertension in young women, we reviewed the medical records of all women aged 15 to 44 years who were hospitalized in any of 15 affiliated hospitals from 1971 to 1980 with malignant hypertension. There were 15 new patients in this period, an incidence of 0.5 per 100,000 women of these ages per year. Four women had underlying renal disease. All of the remaining 11 used oral contraceptive smoked cigarettes, or both. Nine were white, ar 6 women had normal blood pressure in the 2 months before hospitalization. These findings su port a relation of oral contraceptive use and cig rette smoking to an increased risk of malignant h pertension in young women.

We studied the factors associated with malignant hypertension in women aged 15 to 44 years. We did so because a number of case reports of malignant hypertension in oral contraceptive users have appeared,[1–11] but the frequency of the condition in young women is unknown.

Methods

We used computer-stored hospital discharge records from a multihospital database for the years 1971 through 1980 to identify women aged 15 to 44 years who were hospitalized with a diagnosis of malignant hypertension (ICDA-8 Codes 430.0-430.9). After reviewing their medical records, we retained in this series only nonpregnant women with a first diagnosis of malignant hypertension, as characterized by very high blood pressure (BP) (diastolic >160 mm Hg or systolic >220 mm Hg) and papilledema with retinal hemorrhages or exudates or renal or cardiac failure. The medical records were used to determine race, oral contraceptive use, cigarette smoking, a history of systemic hypertension, and most recent pre-illness BP.

The denominator used to calculate the incidence rate of malignant hypertension was the number of woman-years of observation in the population served by the hospitals among women 15 to 44 years old for 1971 to 1980.

Results

Fifteen women aged 15 to 44 years had a first diagnosis of malignant hypertension in the years 1971 to 1980. The incidence of the disease in this age group was 0.5 cases per 100,000 women per year. Four of t women had an underlying disease: 1 chronic glomer lonephritis, 1 lupus erythematosis, 1 scleroderma, a 1 right renal artery stenosis due to fibromuscular dy plasia. Two of these women smoked cigarettes and o used oral contraceptives.

Table I describes the 11 women who had maligna hypertension and no underlying disease. All of the either used oral contraceptives, smoked cigarettes, both. Nine were white. Five had normal BP measu ments documented in the medical record in the months before admission and another had been told a physician that her BP was "normal" 4 months bef admission.

Discussion

Malignant hypertension is very rare in women childbearing age in this population. In this series, as others,[12] many of the patients with malignant hyp tension had an underlying disease. Of particular inter here are the characteristics of the patients witho underlying disease: all of them used oral contraceptiv smoked cigarettes, or both. Many had normal BP bef the onset of the disease; only one was black. Pr studies[12] have emphasized malignant hypertension a complication of renal or hypertensive disease, though its infrequent occurrence in the absence of eit had been recognized.[13,14] Our data suggest that in you women, a large subset of cases of the disease occurs women who were entirely healthy until its occ rence.

A fairly large number of oral contraceptive users w malignant hypertension have been reported in t medical literature,[1–11] although an epidemiologic stu

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TABLE I Description of Women With Malignant Hypertension and No Underlying Disease

Patient	Age (yr)	Race	Oral Contraceptive Use	Cigarette Smoking (packs/day)	History of Hypertension	Blood Pressure In 24 Months Before Hospitalization (mm Hg)
1	39	White	Past*	Never	†	210/110
2	43	White	Never	Now (2+)	†	130/90
3	35	White	Never	Now (1–2)	0	. . .
4	36	White	Never	Now (1–2)	†	110/70
5	41	White	Never	Now (2+)	0	160/100
6	42	Black	Never	Now (1–2)	0	140/86
7	34	White	Now	Never	0	120/60
8	27	White	Now	. . .	0	120/60
9	38	White	Now	Now (<1)	†	160/105
10	31	Oriental	Now	Never	0	114/82
11	39	White	Now	Now (. . .)	0	"Normal"

* Oral contraceptives stopped 8 months before admission because of high blood pressure.
† History of hypertension associated with oral contraceptive use only.

of the condition has not been done. Based on data from surveys of use of birth control methods among adult women in the United States in the 1970s,[15] we estimate that 2 oral contraceptive users would be expected among 11 women the ages of our patients. Thus, this study provides evidence that the risk of malignant hypertension is increased in oral contraceptive users.

The relation of malignant hypertension to cigarette smoking has been reported.[16,17] Our data provide support for a relation to smoking: 7 of 11 patients with the disease were smokers, although only 4 would be expected based on natural estimates of the percentages of cigarette smokers in women.[18]

The pathogenesis of malignant hypertension is not known with certainty. Linton,[19] Isles,[16] Kincaid-Smith,[20] Gavras,[21] and their co-workers suggested similar explanations: Vessel injury sets off intravascular coagulation, either accompanied or caused by microangiopathic hemolytic anemia, and the intravascular coagulation then perpetuates the vessel injury, setting up a vicious cycle. The importance of a relationship between oral contraceptive use and malignant hypertension in the context of this mechanism lies in observations that oral contraceptive use is associated with hypercoagulability, manifested in an increase in the risk of thromboembolic disease,[22,23] and with intimal vascular lesions.[24]

Both oral contraceptives[25] and smoking[26] are associated with lower concentrations of a stable metabolite of prostacyclin (PGI_2), one role of which is to limit the extent of thrombus formation at sites of endothelial injury. Untreated hypertensive patients have a higher concentration of a stable metabolite of PGI_2, which reverts to normal when blood pressure is lowered pharmacologically.[27] Roy et al[27] suggest that enhanced vessel wall PGI_2 synthesis may protect against organ damage in patients with hypertension. Perhaps smokers, oral contraceptive users, and small subgroups of hypertensive patients who have impaired vessel wall PGI_2 synthesis or enhanced degradation have malignant hypertension because of the absence of this protective mechanism. We cannot confirm this hypothesis, but we believe further research on malignant hypertension might explore an alteration in PGI_2 regulation, production, or degradation as a mechanism underlying the

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Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Prescribing Information

Tablets of 50 mg
Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions Impaired Hepatic or Renal Function: The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications**, **Warnings**, and **Precautions**.

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings**.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

Printed in U.S.A. C83-16 (Rev. 5/83)

GEIGY Pharmaceuticals
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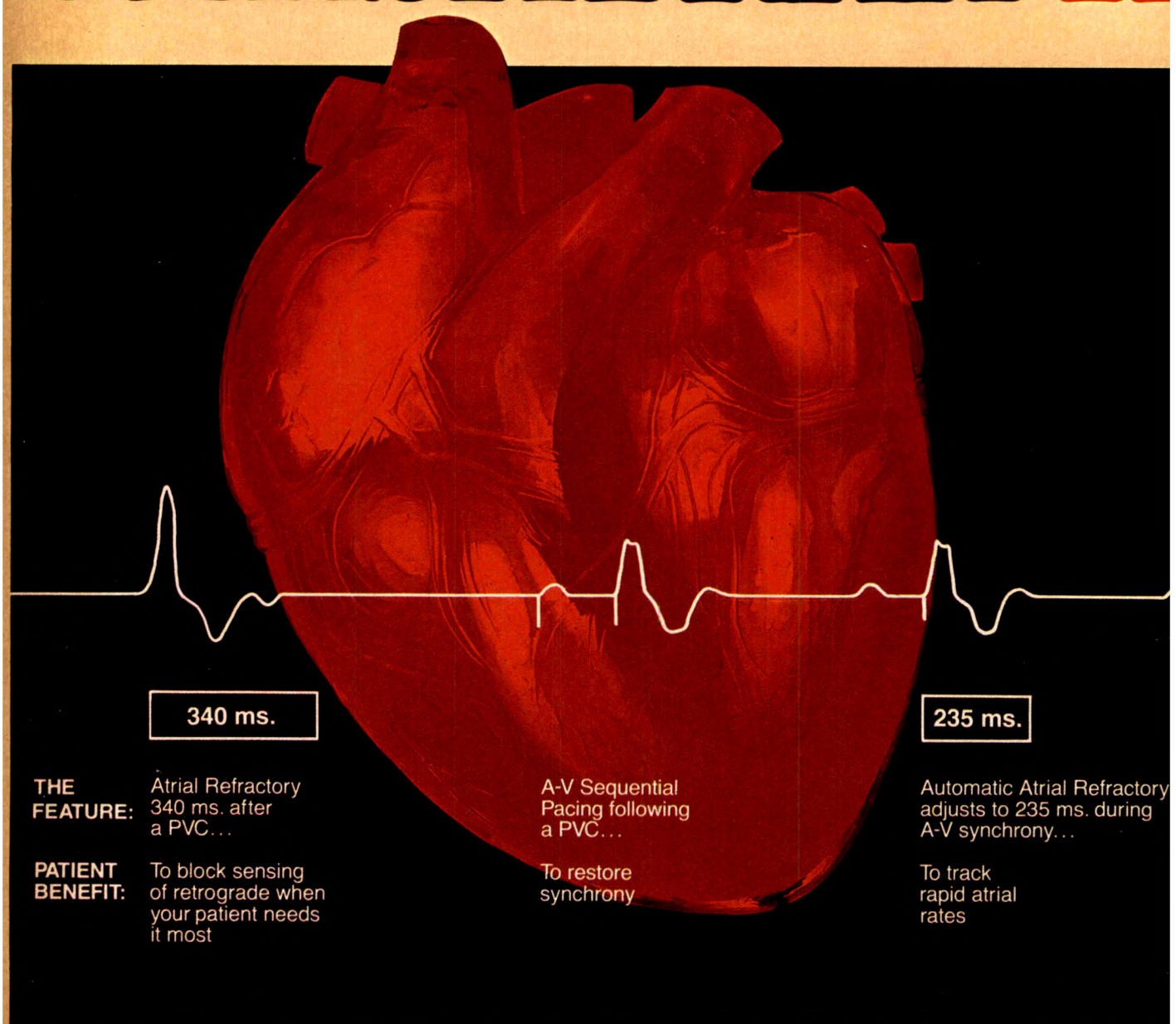
The original cardioselective* beta blocker...
is now...
Lopressor® (metoprolol tartrate)
exerts a preference for beta-one receptors; this preference is not absolute.
*Lopressor® (metoprolol tartrate) exerts a preference for beta-one receptors; this preference is not absolute.
Lopressor® (metoprolol tartrate) 100-day

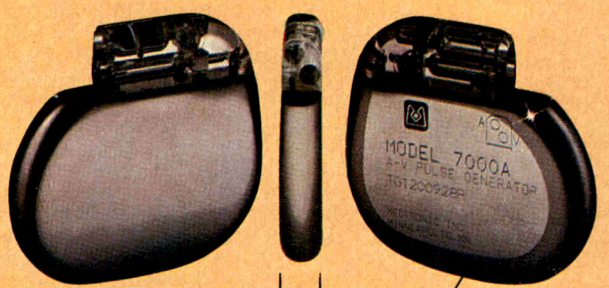
New VERSATRAX II



	340 ms.		235 ms.
THE FEATURE:	Atrial Refractory 340 ms. after a PVC...	A-V Sequential Pacing following a PVC...	Automatic Atrial Refractory adjusts to 235 ms. during A-V synchrony...
PATIENT BENEFIT:	To block sensing of retrograde when your patient needs it most	To restore synchrony	To track rapid atrial rates

Keeps a heart beating like a heart.

The most physiologic pacemaker.



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Versatrax™ II Model 7000A Universal A-V Pacemaker

Intended Use

The Model 7000A universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing where restoration of A-V synchrony and/or sinus modulated rate variability is indicated to improve cardiac output or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

NOTE: The Medtronic® Model 7000A universal A-V pulse generator is under clinical investigation in the U.S. The procedures for using this pulse generator, as well as its safety and efficacy, will be evaluated during this investigational study according to the Clinical Investigation Protocol. Therefore, the "Intended Uses" section is based on Medtronic's experience with other physiologic pulse generators. No claims for safety and efficacy can be made for the Model 7000A pulse generator during its clinical investigation. Patients should be advised that the Model 7000A pulse generator is under clinical investigation.

Contraindications

General: There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode: The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

DVI Mode: In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy: Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site.

Electrosurgical Units: Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

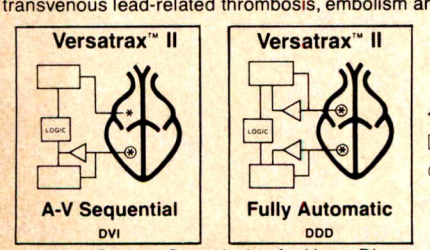
Defibrillation: Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. Positioning a magnet or the programming head over the pulse generator makes it subject to programming. A nominal vertical magnetic field strength of 90 Gauss (in a field measured 1½ inches from the magnet's surface) from a magnet at 1¼ inches from the reed switch is required to initiate asynchronous pacing. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pulse generator. If an electrocautery unit is used, the physician may prefer to program the pacemaker to asynchronous pacing prior to the procedure.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.



KEY TO SYMBOLS

◁ = Sensing Circuit
□ = Output Circuit
○ = Sensing
* = Stimulation

Inter-Society Commission for Heart Disease Research Code.

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INFECTIONS
IN THE ABNORMAL HOST

Edited by Michael H. Grieco, M.D.
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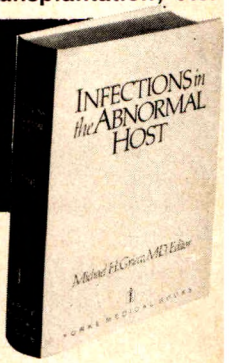

Infections in the Abnormal Host discusses in 36 revealing chapters the mechanics of host defenses . . . the various underlying disorders and the latest treatments by chemotherapy, management of agranulocytosis, immunological reconstitution, passive and active immunotherapy, and immunostimulation.

Consultation and study of **Infections** will help you understand, diagnose, and manage the many infections which strike patients whose defense mechanisms are down.

Check this list of chapters

PART I HOST DEFENSES

• Introduction to the Abnormal Host and Complicating Infections • The Neutrophil in Host Defense: Congenital, Acquired and Drug-induced Abnormalities • The Complement System in Human Disease • Structure and Function of Immunoglobulins • Human Lymphocyte Subpopulations: Surface, Intracellular, Enzymatic Markers and Functions • Congenital and Acquired Primary Disorders of B and T Lymphocyte Function • Drug-induced B and T Lymphocyte and Monocyte Dysfunction • Cutaneous, Pulmonary, Gastrointestinal and Genitourinary Defense Mechanisms and Relationship to Nosocomial Infections • The Effects of Malnutrition on Host Responses and the Metabolic Sequelae of Infections • Humoral and Cellular Responses to Infection

PART II INFECTIONS ASSOCIATED WITH THE ABNORMAL HOST

• Pyogenic Bacterial Infections • Higher Bacterial and Fungal Infections • Mycobacterial Infections • Viral and Chlamydial Infections • Protozoal and Helminthic Infections • Infections Complicating the Transfusion of Blood, Blood Products, Animal Exposure and Animal Products • Infections Complicating the Alcoholic Host • Infections in Parenteral Narcotic and Drug Abusers • Infections Complicating Uremia and Organ Transplantation • Infections in Patients with Neoplastic Diseases • Infections Complicating Diabetes Mellitus • Diagnosis and Treatment of Diffuse Pneumonias • Host Deficiency States and Central Nervous System Infections • Genitourinary Infections • Infections Complicating the Rheumatic Diseases • Endovascular and Prosthetic Implant Infections • Intraocular Manifestations of Systemic Infections • Selected Histopathologic Responses • The Microbiology Laboratory in Diagnosis and Therapy • Infections Complicating Surgical or Functional Splenectomy and Gastrectomy

PART III MANAGEMENT

• Antimicrobial Therapy in the Compromised Host: Resistance, Pharmacology and Toxicity • Chemotherapy for Viral and Chlamydial Infections • Chemotherapy for Protozoal and Helminthic Infections • Infection Prevention in Patients with Cancer and Granulocytopenia • Immunologic Reconstitution • Gamma Globulin and Vaccine Therapy • Index

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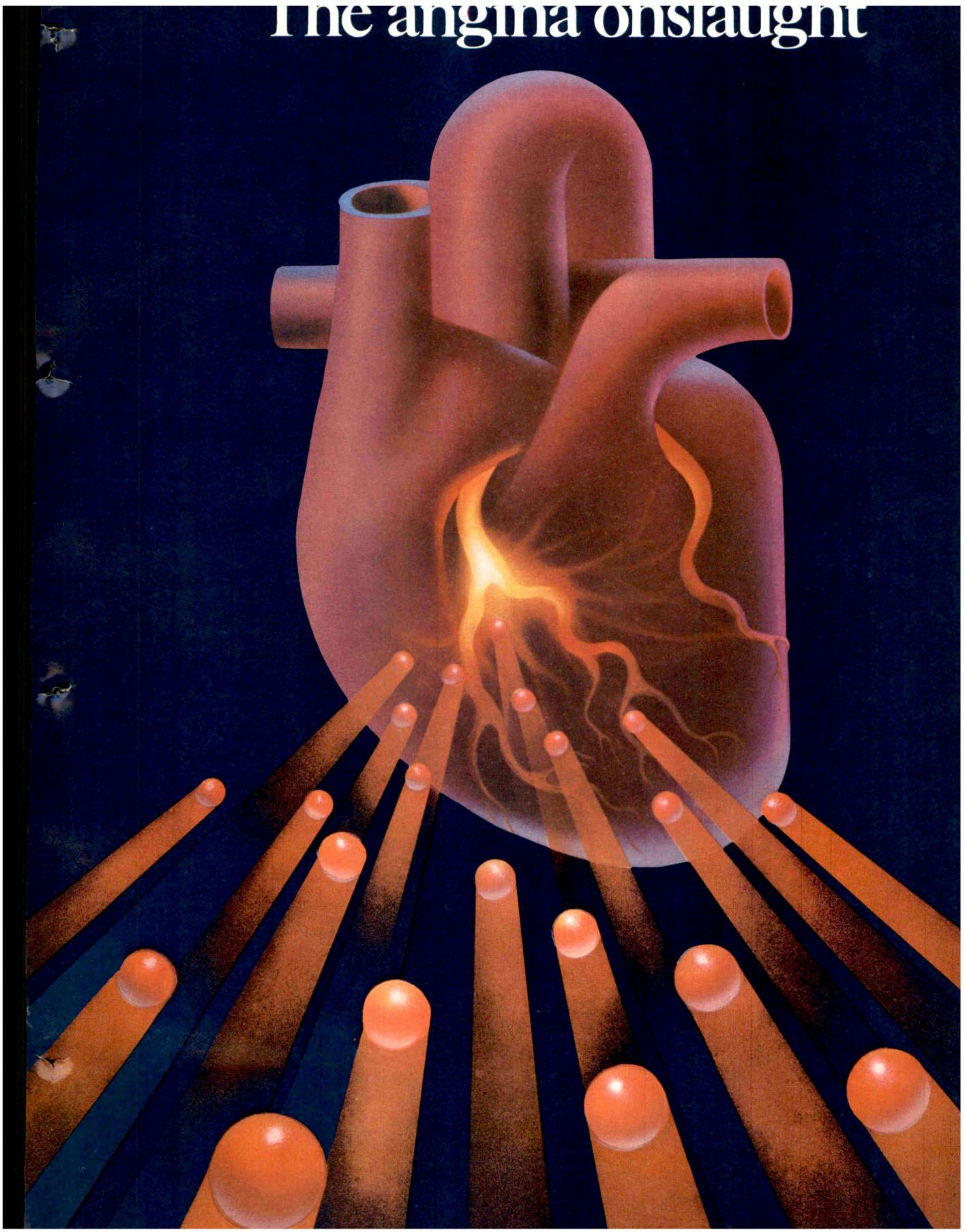
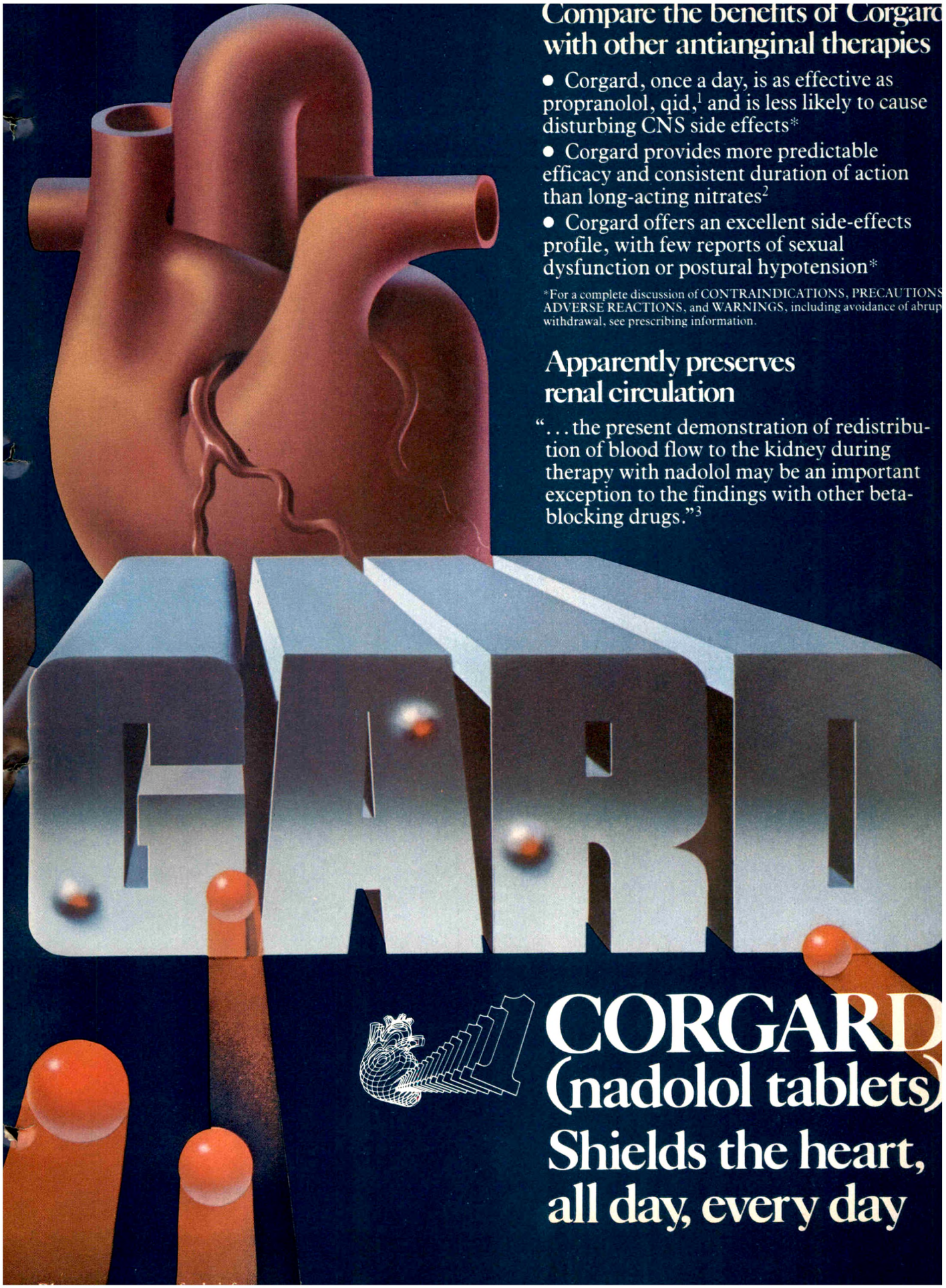
The angina onslaught



The angina shield:
CORGARD®
(nadolol tablets)

SQUIBB®


Compare the benefits of Corgard with other antianginal therapies
• Corgard, once a day, is as effective as propranolol, qid,[1] and is less likely to cause disturbing CNS side effects*
• Corgard provides more predictable efficacy and consistent duration of action than long-acting nitrates[2]
• Corgard offers an excellent side-effects profile, with few reports of sexual dysfunction or postural hypotension*
*For a complete discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, see prescribing information.
Apparently preserves renal circulation
"...the present demonstration of redistribution of blood flow to the kidney during therapy with nadolol may be an important exception to the findings with other beta-blocking drugs."[3]
GARD
CORGARD
(nadolol tablets)
Shields the heart, all day, every day

CORGARD®
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Once a day for angina pectoris

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

References: 1. Data on file, Squibb Institute for Medical Research. 2. O'Rourke RA: Treatment of angina pectoris with beta-blocking drugs. In Current Concepts in Beta-Adrenergic Blockade in the Management of Hypertension and Angina Pectoris. Symposium Proceedings, San Francisco, Sept 5-7, 1979, pp. 54-61. 3. Textor SC, Fouad FM, Bravo EL, et al: Redistribution of cardiac output to the kidneys during oral nadolol administration. N Engl J Med 307:601-605, 1982.

SQUIBB

Determinants of Circulatory Response to Intravenous Hydralazine in Congestive Heart Failure

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J. SANFORD SCHWARTZ, MD, NANCY FERRARO, RN, and NATHANIEL REICHEK, MD

To determine whether the circulatory response to hydralazine in heart failure is influenced by initial hemodynamic status or left ventricular (LV) chamber size, 28 patients with chronic LV dysfunction were studied. Hemodynamic measurements and echocardiographic LV end-diastolic dimension were correlated with the response to 20 mg of intravenous hydralazine and to a dose titrated in each patient to reduce systemic resistance by ≥20%. Hydralazine, 20 mg, decreased systemic resistance from 23 ± 8 to 18 ± 8 U ($p < 0.01$) and increased the cardiac index from 2.0 ± 0.5 to 2.5 ± 0.6 liters/min/m² ($p < 0.01$) and the stroke work index from 21 ± 11 to 24 ± 9 g·m/m² ($p < 0.05$). Titrating the dose to decrease systemic resistance by ≥20% increased the cardiac index further to 2.7 ± 0.6 liters/min/m² and the stroke work index to 32 ± 9 g·m/m². The change in systemic resistance produced by 20 mg of hydralazine correlated only with initial systemic resistance ($r = 0.53$), suggesting that vascular response to hydralazine is a direct function of initial vascular resistance. The percentage change in stroke work index produced by 20 mg of hydralazine correlated directly with indexes of LV preload–end-diastolic wall stress ($r = 0.69$) and pulmonary wedge pressure ($r = 0.43$) and inversely with stroke work index ($r = -0.49$), an index of ventricular work. Similar but less close correlations were observed when the dose of hydralazine was titrated. The hemodynamic response to hydralazine did not correlate with LV end-diastolic dimension or right atrial pressure. Thus, vascular response to moderate doses of hydralazine is related to initial systemic vascular resistance. LV pump response is related to the level of initial LV pump dysfunction but not to LV chamber size or right atrial pressure.

Hydralazine is a direct smooth muscle vasodilator widely used in the treatment of patients with congestive heart failure (CHF). This agent usually augments cardiac output and stroke work in such patients.[1–4] However, in a substantial subgroup of patients, hydralazine produces little or no hemodynamic improvement.[2,3] Accordingly, there has been growing interest in identifying physiologic or pharmacologic factors that determine a patient's response to hydralazine, so that patients most likely to benefit from hydralazine can be identified.[4]

The present study investigates whether the vascular and left ventricular (LV) pump response to moderate doses of hydralazine in patients with heart failure is related to their initial circulatory status or to LV chamber size. Intravenous hydralazine was used to avoid potential problems with variable gastrointestinal absorption of the agent. Vascular responsiveness was assessed by examining the effect of 20 mg of intravenous hydralazine on systemic vascular resistance. The LV pump response was assessed by examining changes in pump function indexes in response to 20 mg of hydralazine and in response to a dose of hydralazine titrated to decrease systemic resistance by ≥20%.

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Methods

Patients: Twenty-eight patients, 15 men and 13 women, with chronic LV dysfunction were studied. All patients had a history of exertional breathlessness or fatigue, or both, during normal daily activities despite administration of digoxin and diuretics (New York Heart Association functional class III or IV). LV dysfunction was attributed to coronary artery disease in 17 patients and to idiopathic dilated cardiomyopathy in 11. The ejection fraction averaged 22 ± 8%. No patient had primary valvular disease, myocardial infarction within the previous 3 months, or worsening of their CHF within the previous 2 weeks. All patients were receiving stable doses of digoxin and furosemide and had not received any vasodilators for at least 2 weeks.

Protocol: An M-mode echocardiogram was obtained within 24 hours of hemodynamic studies using a commercially

TABLE I Hemodynamic Responses to a 20-mg Dose of Intravenous Hydralazine and to an "Effective Dose" (Dose That Decreased Systemic Vascular Resistance ≥20%)

		Hydralazine	
	Control	20 mg	Effective Dose
Heart rate (beats/min)	87 ± 14	87 ± 13	87 ± 11
Mean arterial pressure (mm Hg)	83 ± 13	76 ± 9*	76 ± 10*
Pulmonary wedge pressure (mm Hg)	21 ± 8	20 ± 9†	21 ± 9
Cardiac index (liters/min/m^2)	2.0 ± 0.5	2.5 ± 0.6*	2.7 ± 0.6*
Stroke volume index (ml/beat/m^2)	24 ± 7	31 ± 9*	26 ± 10*
Stroke work index (g·m/m^2)	21 ± 11	24 ± 9†	32 ± 9†
Systemic vascular resistance (U)	23 ± 8	18 ± 8*	15 ± 3*

* $p < 0.01$.
† $p < 0.05$.

available ultrasonoscope. The left ventricle was visualized and recorded at the high chordal level. LV end-diastolic dimension and posterior wall thickness were measured at the peak of the R wave. Echocardiograms were evaluated by one investigator without knowledge of the patient's clinical or hemodynamic status. Echocardiograms were measured with a digitizer and programmable computer. Three to 5 sequential cardiac cycles were measured and the values averaged. Relative wall thickness was calculated as 2 times the posterior wall thickness/LV end-diastolic dimension. Technically adequate echocardiograms were obtained in 26 of the 28 patients.

The following day, a thermodilution Swan-Ganz catheter was inserted and advanced to the pulmonary artery. A short polyethylene catheter was inserted into a radial artery. Duplicate baseline measurements were made of right atrial pressure, pulmonary artery pressure, pulmonary wedge pressure, and cardiac output. Cardiac output was determined in triplicate using injection of iced dextrose and a thermodilution cardiac output computer.

The response to a 20-mg dose of intravenous hydralazine was assessed in all patients. Intravenous hydralazine, 10 mg, was administered. Fifteen minutes later, an additional 10 mg was administered. Preliminary studies indicated that the peak effect of hydralazine is observed within 30 minutes after a dose. Therefore, all hemodynamic measurements were repeated 15, 30, and 40 minutes after the second dose of hydralazine. Measurements at 30 and 40 minutes were virtually identical. Therefore, measurements made at 40 minutes were used to assess the hemodynamic response to hydralazine.

The response to an effective dose of hydralazine was also assessed. An effective dose was defined as that dose which decreased systemic vascular resistance ≥20%. The effective dose was identified by administering additional 10-mg doses of intravenous hydralazine every 30 minutes until systemic vascular resistance decreased ≥20% or a total dose of 50 mg of hydralazine was achieved. Hemodynamic measurements were made at the end of each 30-minute period. The effective dose of hydralazine averaged 27 ± 7 mg (range 10 to 40). One patient had no hemodynamic response to 50 mg of intravenous hydralazine.

Calculated variables: Mean arterial pressure was determined by electronic filtration. Systemic vascular resistance (SVR) was calculated as (mean arterial pressure − mean right atrial pressure)/cardiac output. Cardiac index was calculated as cardiac output/body surface area, and stroke volume index as cardiac index/heart rate. Stroke work index (SWI) was calculated as stroke volume index · 0.0136 · (mean arterial pressure − pulmonary wedge pressure). End-diastolic LV stress was estimated as (0.334 · pulmonary wedge pressure· echocardiographic LV diastolic dimension)/[wall thickness (1 + wall thickness/LV diastolic dimension)].[5]

Statistical evaluation: All values are expressed as mean ± standard deviation. Differences between control and posthydralazine measurements were compared using Student's t test for paired data. The hemodynamic response to hydralazine was expressed as the absolute and percentage changes in SVR, cardiac output, and SWI. The relation between these responses and initial physiologic parameters was examined by linear regression analysis using the least-squares method. The following initial physiologic parameters were correlated with hemodynamic response: ejection fraction, cardiac index, stroke volume index, SWI, heart rate, systolic blood pressure, mean blood pressure, right atrial pressure, pulmonary wedge pressure, SVR, LV end-diastolic wall stress, LV diastolic dimension, and LV relative wall thickness. A p value <0.05 was considered significant.

Results

Control hemodynamic measurements revealed a mean resting cardiac index of 2.0 ± 0.5 liters/min/m^2, mean pulmonary wedge pressure of 21 ± 8 mm Hg, mean right atrial pressure of 5 ± 8 mm Hg (range 1 to 15), mean SVR of 23 ± 8 U (range 14 to 35 U), and mean LV end-diastolic dimension of 6.6 ± 1.2 cm (range 4.7 to 9.2).

Circulatory responses: Hemodynamic responses to a 20-mg dose of hydralazine and to an effective dose of hydralazine are summarized in Table I and illustrated in Figure 1. After administration of 20 mg of hydralazine, SVR decreased <20% in 10 patients, 20 to 40% in 15, and >40% in 3, indicating a variable direct vascular response to hydralazine. This vasodilation was associated with an increase in cardiac output of ≥20% in 18 patients (64%), whereas an increase in SWI of ≥20% occurred in only 10 patients (36%). Administration of an effective dose of hydralazine decreased SVR by ≥20% in all but 1 patient and increased cardiac output ≥20% in 22 of the 28 patients (79%). In contrast, the SWI increased ≥20% in only 14 patients (50%).

Determinants of the vascular response to hydralazine: To investigate factors that influence the vascular response to hydralazine, the relation between changes in SVR produced by 20 mg of hydralazine and initial physiologic variables was examined. The change in SVR correlated directly with initial SVR ($r = 0.53$) (Fig. 2). No other variable correlated with changes in SVR (Table II).

Determinants of LV pump response to vasodilation: The percentage change in SWI produced by 20 mg of hydralazine correlated directly with indexes of LV preload–end-diastolic wall stress ($r = 0.69$) and pulmonary wedge pressure ($r = 0.43$) and inversely with initial SWI ($r = -0.49$), an index of LV work (Fig. 3). The percentage change in SWI also correlated inversely with relative wall thickness ($r = -0.44$). Except for the correlation with wedge pressure, these correlations were also present when changes in SWI were expressed in absolute terms (Table II). The percentage change in SWI produced by an effective dose of hydralazine cor-

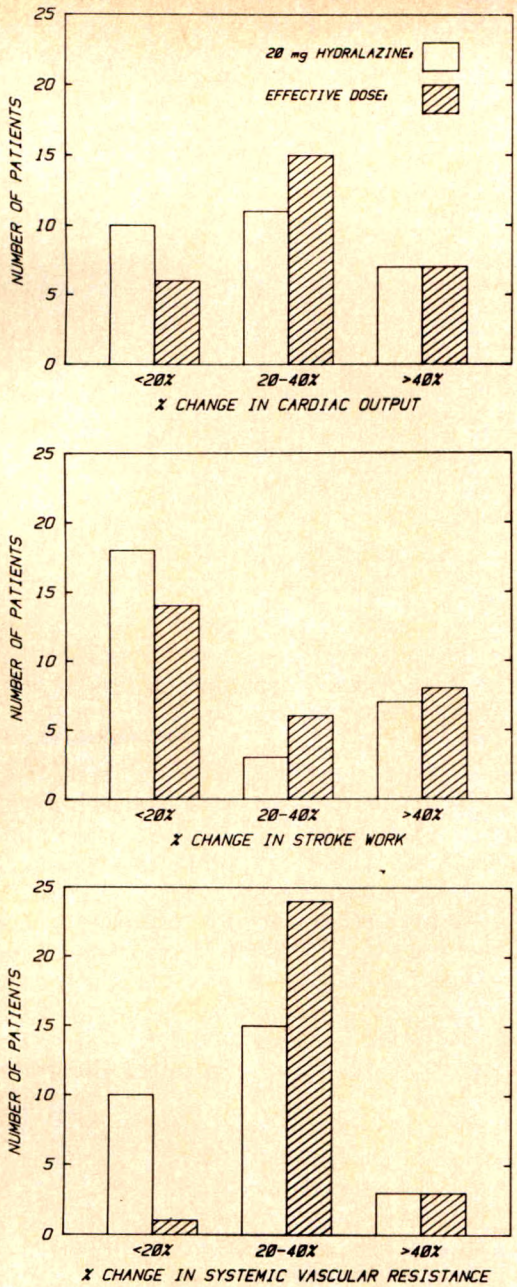

FIGURE 1. Comparison of hemodynamic responses to a 20-mg dose of intravenous hydralazine versus an effective dose of hydralazine.

related with initial SWI (r = −0.44) (Table III). The absolute change in SWI did not correlate with any measured initial physiologic parameters.

The percentage change in cardiac index produced by 20 mg of hydralazine correlated with initial end-diastolic wall stress (r = 0.48). However, this correlation was not significant when the change in cardiac index was expressed in absolute terms (Table II). The percentage change in cardiac index produced by an effective dose of hydralazine did not correlate with initial hemodynamic variables, whereas the absolute change in cardiac index correlated only with ejection fraction (r = 0.45) (Table III).

Discussion

The present study was undertaken to identify physiologic factors that account for the variable circulatory responses to hydralazine noted in patients with chronic CHF. Packer and LeJemtel[4] identified 3 factors that potentially may be responsible for this variability: (1) variations in the direct vascular effects of a drug, (2) variations in LV response to a decrease in peripheral resistance, and (3) variations in the degree to which

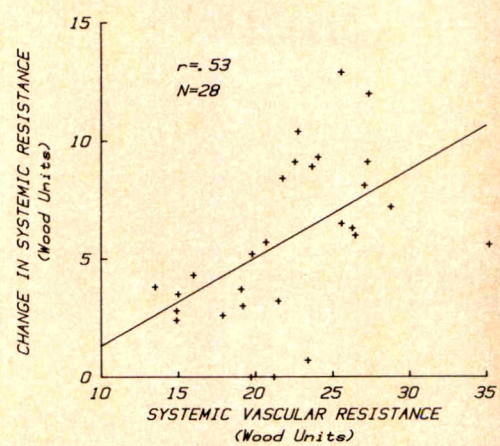

FIGURE 2. Relation between absolute change in systemic vascular resistance produced by 20 mg of hydralazine and initial systemic resistance.

TABLE II Correlations Between Initial Physiologic Variables and Hemodynamic Response to 20 Mg of Hydralazine

	Change in Systemic Resistance		Change in Cardiac Index		Change in Stroke Work Index	
	Absolute	%	Absolute	%	Absolute	%
Cardiac index	−0.06	0.12	0.07	−0.17	−0.28	−0.30
Stroke work index	−0.04	0.02	−0.06	−0.27	−0.47*	−0.49*
Mean blood pressure	0.25	0.18	0.03	−0.09	−0.43†	−0.34
Right atrial pressure	0.25	0.15	0.02	0.10	−0.12	0.02
Wedge pressure	0.31	0.26	0.28	0.37	0.22	0.43†
Systemic resistance	0.53*	0.26	0.16	0.30	0.02	0.11
End-diastolic wall stress	0.24	0.25	0.37	0.48*	0.53*	0.69*
LV end-diastolic dimension	−0.10	−0.01	0.12	0.10	0.22	0.08
Relative wall thickness	0.08	0.08	0.14	−0.19	−0.55*	−0.44†
Ejection fraction	0.05	0.15	0.22	0.16	0.13	0.26

* $p < 0.02$.
† $p < 0.05$.
LV = left ventricular.

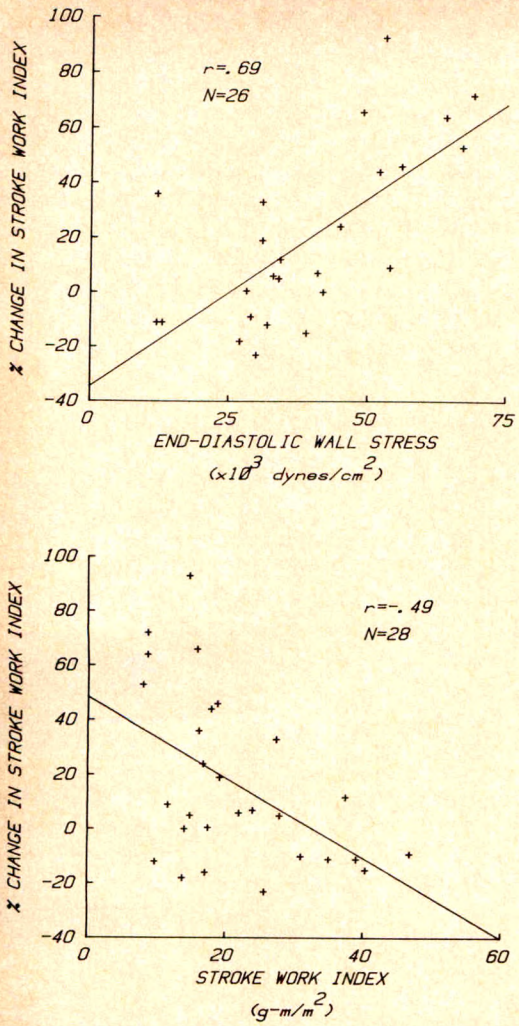

FIGURE 3. Relation between percent change in stroke work index produced by 20 mg of hydralazine and initial end-diastolic wall stress and stroke index.

peripheral vasodilation activates endogenous neurohumoral mechanisms. Accordingly, it is of interest to examine how initial physiologic parameters measured in this study influenced each of these 3 factors.

Determinants of direct vascular response to hydralazine: Vascular responsiveness to hydralazine may be assessed by examining the degree to which a fixed dose of hydralazine alters peripheral vascular resistance. Using this approach, our results indicate that direct vascular responses to hydralazine are quite variable. After a 20-mg dose of hydralazine, 18 patients exhibited a ≥20% decrease in SVR, whereas 10 patients had a <20% decrease.

The only physiologic factor that correlated with the direct vascular effect of hydralazine was initial SVR; the degree to which hydralazine decreased SVR was directly related to initial SVR. This finding is consistent with experimental studies which demonstrated that the magnitude of vasodilation produced by a given stimulus is a linear function of the resistance before stimulation.[6,7]

TABLE III Correlations Between Initial Physiologic Variables and Hemodynamic Response to an Effective Dose of Hydralazine

	Change in Cardiac Index		Change in Stroke Work Index	
	Absolute	%	Absolute	%
Cardiac index	0.13	−0.23	−0.29	−0.32
Stroke work index	0.06	−0.26	−0.29	−0.44*
Mean blood pressure	0.15	−0.03	−0.28	−0.30
Right atrial pressure	0.09	−0.02	−0.02	0.13
Wedge pressure	0.18	0.31	0.07	0.27
Systemic resistance	−0.06	0.27	−0.07	−0.07
End-diastolic wall stress	0.18	0.35	0.21	0.38
LV end-diastolic dimension	0.06	0.07	0.29	0.22
Relative wall thickness	0.07	−0.14	−0.29	−0.20
Ejection fraction	0.45*	0.37	0.14	0.29

* $p < 0.05$.
LV = left ventricular.

Recently, it has been suggested that venous pressure also may influence vascular responsiveness to hydralazine[2]; the dose of oral hydralazine required to produce vasodilation correlated inversely with right atrial pressure. In the present study, no relation between vascular response to hydralazine and right atrial pressure was noted. Therefore, it is likely that venous pressure correlates with the hemodynamic response to oral hydralazine because of an association with drug absorption rather than vascular responsiveness.

Determinants of LV pump response to vasodilation: There are several ways to examine the LV pump response to peripheral vasodilation. The pump response to a fixed dose of hydralazine can be examined. Alternatively, the pump response to a dose of hydralazine that produces a given degree of peripheral vasodilation can be examined.

Our findings indicate that regardless of which of these 2 approaches is used, the LV pump response to peripheral vasodilation varies widely. Our findings further suggest that the response may be related to the initial level of LV pump dysfunction. Changes in SWI after 20 mg of hydralazine were directly related to indexes of LV preload, end-diastolic wall stress and pulmonary wedge pressure, and inversely related to SWI, an index of cardiac systolic performance. Thus, patients with the most severe cardiac dysfunction as evidenced by high preload and low systolic performance tended to respond most favorably to vasodilation. Less close correlations between physiologic variables and hemodynamic responses were noted after an effective dose of hydralazine, although the findings were generally consistent with this conclusion.

Correlations between initial hemodynamic parameters and the response to hydralazine, however, were not sufficiently close to provide clinically useful predictive information about an individual patient's response to hydralazine. Moreover, several of these correlations were between an initial parameter and a change in that parameter. Because the initial parameter influences the calculation of the change, such correlations involve

dependent variables and thus must be interpreted cautiously. Therefore, it is likely that the response to hydralazine is not a simple function of 1 circulatory factor. This finding is not unexpected because the coupling between the peripheral circulation and LV afterload is complex. For example, a given perturbation in systemic resistance may have different effects on central blood pressure and, therefore, on LV afterload depending on arterial impedance and baroreceptor activity.

In contrast to our findings, Packer et al[2] noted a relatively close linear correlation between the hemodynamic response to an effective dose of hydralazine and initial LV end-diastolic dimension. LV end-diastolic dimension is an important determinant of LV wall stress, whereas left ventricles with high wall stress are more sensitive to afterload manipulation.[8] Accordingly, these investigators suggested that LV diastolic dimension influences LV pump response to vasodilation due to its relation to wall stress.

The findings of Packer et al[2] are not necessarily inconsistent with our results. Packer et al induced more marked vasodilation in their patients, as evidenced by average decreases in mean arterial pressure of 9 mm Hg in patients with LV end-diastolic dimensions >6 cm and of 16 mm Hg in those with dimensions ≤6.0 cm. In addition, the average SVR after hydralazine was 12.5 U, versus 15 to 18 U in the present study. It is possible that when vasodilation is moderate, as in the present study, LV end-diastolic dimension does not correlate with hemodynamic response. However, when more marked vasodilation is produced, LV end-diastolic dimension does correlate with hemodynamic response.

In any event, the degree of arterial pressure reduction produced in the study of Packer et al[2] is usually not tolerated by patients with CHF due to orthostatic dizziness. Moreover, such reduction in arterial pressure may activate endogenous neurohumoral mechanisms that counteract potentially beneficial hemodynamic effects.[9] Therefore, hydralazine is usually administered clinically in doses that do not produce marked reductions in arterial pressure.[10,11] Our data suggest that LV end-diastolic dimension is not a useful predictor of a patient's hemodynamic response to such dosages.

Hemodynamic response to hydralazine and neurohumoral activation: The degree to which hydralazine activates endogenous neurohumoral mechanisms was not specifically examined in this study. However, it is likely that the degree of activation was modest, if present at all, because mean blood pressure decreased only slightly and no substantial increases in heart rate were observed.

Clinical importance of assessing circulatory response to hydralazine: The clinical importance of identifying the degree of hemodynamic response to hydralazine remains uncertain; a correlation between acute hemodynamic response and long-term clinical response has been observed by some investigators[2,3] but not by others.[12] However, there is agreement that patients who exhibit no acute improvement in pump function with hydralazine usually have no long-term clinical improvement.[2,3,12] Therefore, at the very least, identification of factors that characterize nonresponders to hydralazine is of clinical interest.

Clinical implications: This study indicates that both the direct vascular and the LV pump response to hydralazine is extremely variable in patients with heart failure. Therefore, patients with clinical CHF represent a very heterogeneous population with respect to both their peripheral vasculature and the manner in which the peripheral vasculature is coupled with the left ventricle. This heterogeneity may account for some variability in clinical response to long-term vasodilator therapy.

Our findings further suggest that patients with the highest initial peripheral vascular resistance and most severe pump dysfunction are most likely to exhibit a favorable acute hemodynamic response to moderate doses of hydralazine. However, no correlations between hemodynamic responses and initial physiologic variables were sufficiently close to serve as useful clinical predictors of an individual patient's circulatory response to hydralazine. Therefore, in patients with chronic CHF, initiation of hydralazine should probably be performed in conjunction with hemodynamic monitoring to assure that a patient is responsive to hydralazine. If a patient does not respond acutely to hydralazine, another vasodilator should probably be used instead.

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Amrinone Therapy for Congestive Heart Failure in Outpatients With Idiopathic Dilated Cardiomyopathy

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Amrinone, 100 mg orally every 8 hours, was administered to 13 patients with moderate-to-severe congestive heart failure (CHF) for 1 month on an outpatient basis to determine the beneficial and undesirable effects of this new cardioactive agent in this clinical setting. These subjects received conventional CHF medications during the course of study. Ten patients who received conventional CHF medications alone served as a control group. Changes in functional classification were not significantly different between the 2 treatment groups. Amrinone augmented exercise capacity 37% above baseline compared with a 12% improvement for the control group. Noninvasive indexes of resting left ventricular function (echocardiography and systolic time intervals) did not change significantly for either group, nor was there a significant change in the exercise ejection fraction. All patients treated with amrinone had ≥1 symptom-related or laboratory-detected adverse effect. An increase in the frequency of ventricular ectopic beats was noted at rest in 4 and with exercise in 6 patients (salvos of nonsustained ventricular tachycardia in 2). Six subjects treated with amrinone had gastrointestinal symptoms and 8 developed a viral-like illness. Other adverse effects noted in the amrinone-treated group included near-syncope, headaches, marked anxiety, chest pain, palpitations, maculopapular rash, hypokalemia, and elevation of serum transaminase levels. The control patients had significantly fewer adverse effects.

Although individual patients with CHF may benefit from long-term amrinone therapy, the low benefit-to-risk–adverse effect ratio does not warrant widespread application of this drug in the outpatient management of CHF and requires caution when prescribing.

The therapy of chronic, low-output congestive heart failure (CHF) is a formidable clinical problem. The treatment of CHF is generally directed at reducing congestion (diuretics and preload-reducing vasodilators) and augmenting cardiac output (inotropic agents and afterload-reducing vasodilators). Digitalis is the only drug used on a long-term basis for its positive inotropic properties, but its effectiveness and safety remain controversial. A more effective nonparenteral positive inotropic drug would play an important role in the management of low-output CHF. Amrinone was developed to fulfill this need.[1,2] Initial studies[3–9] of amrinone in patients with CHF suggest that this compound improves resting and exercise hemodynamic findings. This study was designed to determine the beneficial properties and adverse effects of amrinone in the outpatient management of CHF.

From the Division of Cardiology, Ohio State University College of Medicine, Columbus, Ohio. This study was supported in part by the S. J. Roessler Foundation and the James D. Casto Cardiovascular Research Fund, Columbus, Ohio. Manuscript received February 9, 1983; revised manuscript received May 2, 1983, accepted May 4, 1983.

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Methods

Patients: Twenty-four patients with catheterization-proved idiopathic dilated cardiomyopathy and CHF of moderate severity were studied. These patients were separated into 2 groups: a group of 14 patients who were treated with amrinone while continuing conventional CHF therapy, and a randomly assigned control group of 10 patients who received conventional CHF therapy alone. One patient from the amrinone group had clinical deterioration within 2 weeks of entry and had to be withdrawn from the study and analysis. The clinical characteristics of the remaining 13 amrinone-treated patients and the 10 control patients are presented in Table I. There were no significant differences between the 2 groups in age, sex, or duration and severity of CHF. There was no significant difference in the conventional CHF therapy (drugs and dosage) of the 2 groups.

Protocol: The study was performed in the Human Heart Failure Research Laboratory of the Ohio State University

TABLE I Baseline Clinical Characteristics of the 2 Study Groups

	Amrinone Group	Control Group
Number of patients	13	10
Age in years	49 ± 7	50 ± 9
Male : female	11 : 2	10 : 0
Duration of illness (months)	21 ± 19	20 ± 22
Functional classification (NYHA) II : III : IV	4 : 9 : 0	3 : 7 : 0
Medication		
Patients taking digoxin	13	10
Average dose (mg/day)	0.27 ± 0.08	0.25 ± 0.05
Patients taking furosemide	11	9
Average dose (mg/day)	75 ± 43	72 ± 40
Patients taking vasodilators		
Nitrate preparations*	7	4
Hydralazine	4	2
Patients taking antiarrhythmic therapy	2	2

Values expressed as mean ± standard deviation.
* Oral isosorbide dinitrate or nitroglycerin ointment.
NYHA = New York Heart Association.

Outpatient Clinic. Baseline studies included clinical evaluation (history and physical examination) by 1 of the clinical investigators (CVL or DVU), hematologic and blood chemistry testing, M-mode echocardiography, systolic time intervals, treadmill exercise testing, and resting and exercise radionuclide angiography.

The patients of the amrinone group then began taking ora amrinone, 100 mg every 8 hours, along with the continuatior of their maintenance conventional CHF therapy. The contro patients continued their conventional therapy. The patient returned to the laboratory on a weekly basis for clinical eval uation, symptom and drug recording, and pill counts. Digitali preparations, vasodilators, and doses thereof were not altere during the course of study. Diuretic doses were adjusted ir response to clinical indications (symptoms, physical signs weight). At the end of the 4-week treatment period, eac participant underwent the same studies as those at baseline with cardiac and exercise testing performed 2 hours afte amrinone dosing.

Procedures and measurements: M-mode echocardiog raphy and systolic time intervals were performed with ar Electronics for Medicine Echo IV unit using the technica specifications previously described.[10–12] The echocardio graphic determinants[10,11] of left ventricular (LV) performanc included fractional shortening (% ΔD) and fractional short ening rate (Vcf). The ratio of the preejection period to LV ejection time (PEP/LVET) was used as the systolic time in tervals parameter of LV function.[12]

Treadmill exercise testing, using an Avionics Del Mar 59 treadmill interphased with a Sanborn Hewlett-Packar Visoscope and recorder, was performed in duplicate; th second treadmill was used for baseline data. A modifie Naughton protocol was used for graded exercise testing wit increments in grade, speed, or both occurring every 2 minute 0% 1 mph, 0% 1.5 mph, 3.5% 2 mph, 7% 2 mph, 10.5% 3 mp and 12.5% 3 mph. Fifteen-minute electrocardiographic re

TABLE II Clinical Responses of the 2 Treatment Groups to 4 Weeks of Therapy

	Amrinone Group (n = 13)	Control Group (n = 10)
Functional classification (no. of patients)		
Improvment by ≥1 class	5	3
No change	7	5
Deterioration by ≥1 class	1*	2
Mean change in body weight (kg) (mean ± standard deviation)	−0.61 ± 1.50†	+1.14 ± 1.33‡
Mean change in resting heart rate (beats/min)	6 ± 9†‡	−4 ± 8
Mean change in resting mean systemic blood pressure (mm Hg)	−3 ± 12	−4 ± 9
Undesirable effects (number of patients)		
Palpitations	3	2
Chest pain (new or worsening)	3	1
Increase in ventricular ectopic beats of ≥4/minute		
At rest	4	1
During exercise	6†§	0
Nausea alone	4	0
With vomiting	1 †	0
With diarrhea	1	1
Viral-like illness (coryza, dry or productive coughing, malaise, myalgia, occasional fever and arthralgia)	8†	2
Nocturnal diaphoresis	2	0
Headaches	2	0
Near syncope	4	1
Onset of persistent anxiety with tremors	2	0
Maculopapular rash	1	0
Laboratory abnormalities		
Mean change (±1 standard deviation) in platelet count/mm³ at 1 month	−33,500 ± 38,000†‡	+5,000 ± 17,000
Abnormal elevation of SGOT	1 patient (26 → 178)	0
Severe hypokalemia (≤3.0 mEq/liter)	1‖	0

* An additional patient was dropped from the study and analysis because of marked deterioration of cardiac function and subsequent prolonge hospitalization.
† $p < 0.05$ (amrinone versus control).
‡ $p < 0.05$ (versus baseline).
§ Two of these subjects also had salvoes of ventricular tachycardia (≥3 beats in series) and one patient had frequent paroxysms (duration ≥20 seconds) of supraventricular tachycardia.
‖ This participant required hospitalization for hypokalemia (2.6 mEq/liter) and her first episode of sustained supraventricular tachycardia.
SGOT = serum glutamic oxaloacetic transaminase.

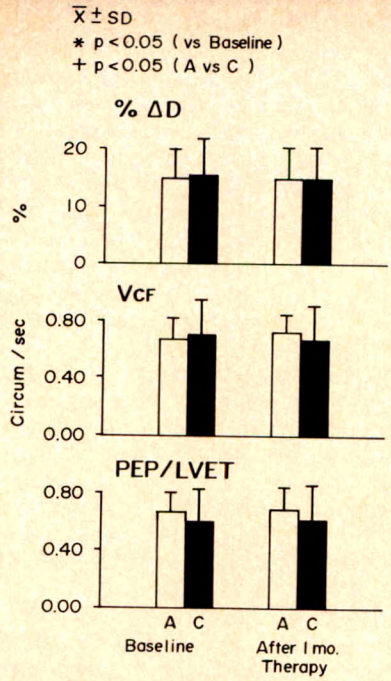

FIGURE 1. Results of echocardiographic (% ΔD and Vcf) and systolic time interval (PEP/LVET) testing at baseline and after 1 month of amrinone (plus conventional therapy) treatment (A) or conventional therapy alone (control group, C). % ΔD = fractional shortening; PEP/LVET = ratio of preejection period to left ventricular ejection time; Vcf = fractional shortening rate.

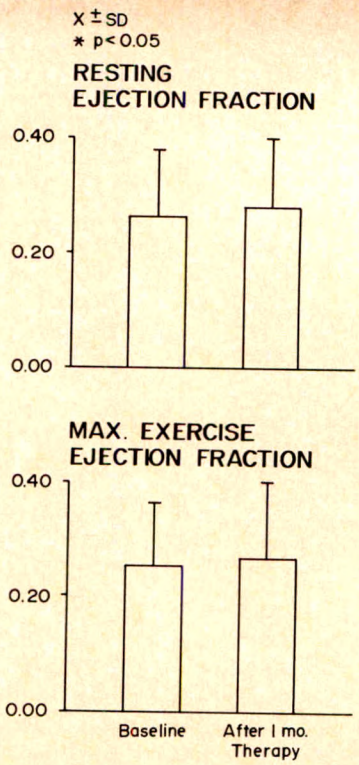

FIGURE 2. Left ventricular ejection fraction, measured at rest (**top**) and at maximal (Max) exercise (**bottom**), did not change significantly after 1 month of amrinone (plus conventional therapy). The ejection fraction was determined by multiple-gated radionuclide angiography.

cordings were obtained before exercise and were continued throughout the exercise period for the determination of heart rate and frequency of ventricular ectopic beats. Maximum exercise capacity was the time at which exercise was stopped because of severe dyspnea or fatigue (symptom-limited maximal exercise) or both.

Exercise radionuclide (technetium-99m pertechnetate) angiography was performed in a standard manner with a Picker Dyna-Mo gamma camera, a Medical Data A^2 40,000 computer system, and a Quinton Uniwork supine bicycle ergometer. Beginning at a work load of 150 kg-m/min, exercise was accomplished in a stepwise fashion with work load increments of 150 kg-m/min every 2 minutes. At maximal exercise, 1 minute of exercise was required before the 2-minute acquisition. The number of radionuclide studies for the control group was insufficient for analysis and therefore were not included.

All technical personnel performing the noninvasive and exercise studies were blinded with respect to treatment. Because it was necessary to adjust and maximize amrinone dosage, the physicians responsible for the clinical care of these patients were not blinded.

Statistical analyses: The clinical and laboratory characteristics of the 2 groups were compared using the Student *t* test for unpaired data and chi-square analysis. Changes within a group between baseline and the 4-week data were analyzed with the Student *t* test for paired data.

Results

Noninvasive cardiac studies and exercise testing: The echocardiographic measurements of LV function (% ΔD and Vcf), the PEP/LVET, and the resting ejection fraction by radionuclide angiography did not change significantly over 1 month of therapy for either group (Fig. 1 and 2).

Four weeks of amrinone therapy effected a significant increase (37%) in maximal exercise capacity above baseline and above that of the parallel control group (12%) (Fig. 3). Heart rate at maximal exercise increased significantly for the amrinone group and averaged +14% above baseline; the control group had little difference in maximal exercise heart rate between baseline and 1-month testing. Changes in mean exercise duration and mean heart rate during bicycle exercise–radionuclide angiography were comparable to those noted during treadmill testing. LV ejection fraction at maximum exercise did not change significantly for the amrinone group after 1 month of treatment (Fig. 2, bottom panel).

Clinical responses (Table II): Five patients of the amrinone group and 3 control patients improved 1 functional classification during the 1-month treatment period. One patient receiving amrinone and 2 control subjects had a deterioration in clinical status. An additional patient was dropped from the amrinone group 10 days after entry because of marked deterioration in his CHF status (pulmonary edema, adult respiratory distress syndrome, and 2 cardiac arrests); improvement coincided with discontinuation of amrinone and the initiation of appropriate supportive measures.

Mean body weight increased 1.14 kg ($p < 0.05$ versus baseline) over the 4-week period for the control group despite an increase in mean furosemide dosage of 39 ± 46 mg. The increase in body weight for the control group was significantly greater than the mean weight change of the amrinone group (−0.61 kg). Mean diuretic dosage

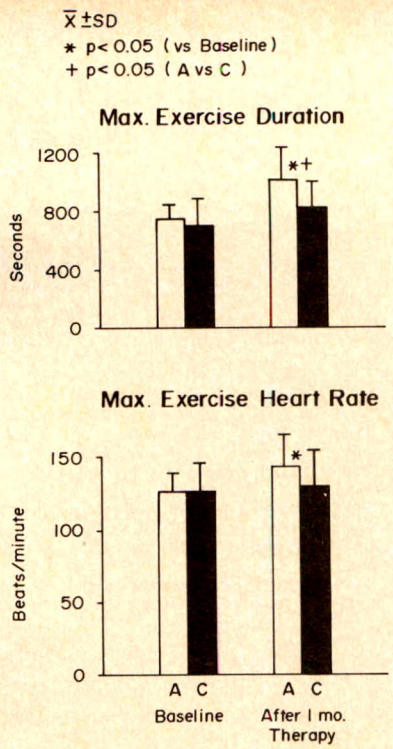

FIGURE 3. Results of treadmill testing for the amrinone (plus conventional therapy) treatment group (A) and the conventional therapy control group (C). Max = maximal.

for the amrinone-treated subjects was not altered during the 1-month course of therapy (1 patient required an increase of 40 mg/day of furosemide; another required a decrease of 40 mg/day).

Resting heart rate for the amrinone group increased significantly above baseline and above that of the control group. Resting mean systemic arterial pressure was not altered for either group.

Four patients of the amrinone group had a documented increase in ventricular ectopic beats (≥4 beats/min) at rest; these patients and 2 others also had an increase in ectopic beats during exercise testing. The exercise study at 1 month was interrupted in 2 subjects treated with amrinone because of short bursts of ventricular tachycardia. In 1 patient, frequent paroxysms of supraventricular tachycardia developed during exercise testing. Another patient, who had no history of cardiac arrhythmia, had hypokalemia (serum potassium level 2.6 mEq/liter) and sustained supraventricular tachycardia within 1 week of initiating amrinone. She had no recurrence of the dysrhythmia after the hypokalemia was corrected despite the continuation of amrinone.

Six patients of the amrinone-treated group complained of gastrointestinal symptoms and 8 had a viral-influenza-like illness. These symptoms lasted 1 to 4 weeks and were treated symptomatically without interrupting amrinone administration. Four of the 6 patients who had gastrointestinal complaints and 4 of 8 who had the viral-like illness during amrinone therapy had a gradual amelioration of these adverse effects by the fourth week. Other symptoms noted during amrinone therapy were palpitations, chest pain, headaches, near-syncope (lightheadedness, dizziness, and blurred vision), persistent marked anxiety, maculopapular rash, and night sweats. Adverse effects were considerably less frequent in the control group.

The mean platelet count decreased by 33,500 platelets/mm^3 ($p < 0.05$) after 1 month of amrinone treatment. The actual nadir in the platelet count generally occurred 1 to 3 weeks after initiation of amrinone therapy and typically returned toward baseline thereafter. The count never dropped below 105,000 platelets/mm^3 for any subject. No evidence of excessive bruising or bleeding occurred during the study period. The serum glutamic oxaloacetic transaminase level increased 7-fold in 1 amrinone-treated patient and returned to baseline within 2 weeks after discontinuing amrinone.

Despite the occurrence of adverse effects, amrinone was continued for 4 weeks in all but 1 patient. At the end of the 4 weeks, 3 more patients were removed from a more long-term phase of amrinone therapy. One of these patients had elevated serum transaminase levels, anxiety and tremors, ventricular ectopic beats at rest, and salvos of ventricular tachycardia during exercise. He had had no ventricular ectopy before amrinone administration and the ectopic beats and exercise-induced ventricular tachycardia abated, as did the elevated transaminase levels, upon stopping amrinone. Amrinone was discontinued in another patient who had chest pain, palpitations, and frequent ventricular and atrial ectopic beats at rest and during exercise; the events abated after amrinone was stopped. The third patient had a viral-like illness, excessive fatigue, and marked dyspnea with amrinone; he improved when the drug was stopped.

Discussion

This study has demonstrated that the addition of standard chronic dosing of amrinone to conventional CHF therapy augments exercise capacity above baseline and above that achieved by patients who receive conventional therapy alone. Whether this improvement in exercise tolerance is maintained beyond 4 weeks is under investigation. The reasons for increased exercise capacity with amrinone are not explained by this study. LV ejection fraction during exercise and the noninvasive indexes of ventricular function, performed at rest, were not improved with chronic amrinone therapy. Increased effort was probably contributory, particularly since heart rate at maximum exercise was higher at 4 weeks.

The patients treated with amrinone also maintained a constant body weight and diuretic dosage compared with the control group who, despite an increase in mean diuretic dosage, gained an average of approximately 1 kg over the 1-month study period. There was no significant difference between the 2 groups in the percentage of patients having improvement, no change, or clinical deterioration. It is unlikely that the lack of dramatic clinical and laboratory improvement with amrinone (plus conventional therapy) was secondary to inadequate dosage, since each of the amrinone-treated subjects experienced 1 or more adverse effects attributable to this agent.

The rather limited beneficial effects of amrinone in our patients with CHF were offset by the frequent occurrence of adverse effects. A high frequency of adverse effects with amrinone was also noted in 5 patients with moderate CHF studied by Dunkman et al.[13] While patients with CHF may have more cardiac and noncardiac symptoms compared with normal human subjects, our study clearly demonstrates that the addition of amrinone to conventional therapy elicits a significant and marked increase in undesirable effects involving the cardiovascular, neurologic, gastrointestinal, hematologic, and dermatologic systems. Thrombocytopenia, a major adverse effect noted previously[5,9] at higher doses of amrinone, was not a major problem during amrinone administration in this study.

How amrinone improves hemodynamic features in CHF is not well understood. Similarly, the mechanisms for the numerous adverse effects are not known. Based upon the high incidence and spectrum of symptom- and laboratory-related adverse effects, it is obvious that amrinone's pharmacologic effects are not confined to the heart or the cardiovascular system. This agent apparently alters the physiology and, in some instances, the biochemistry of several organ systems.

The overall efficacy of continuous amrinone therapy was limited in our patients as a group, and none of the patients had dramatic individual improvement. The frequency of clinical and laboratory adverse effects was high and some were potentially lethal. It is unlikely that amrinone will be widely used in the therapy of CHF.

Acknowledgment: We thank Max Bacher and Mitzi Prosser for their technical assistance.

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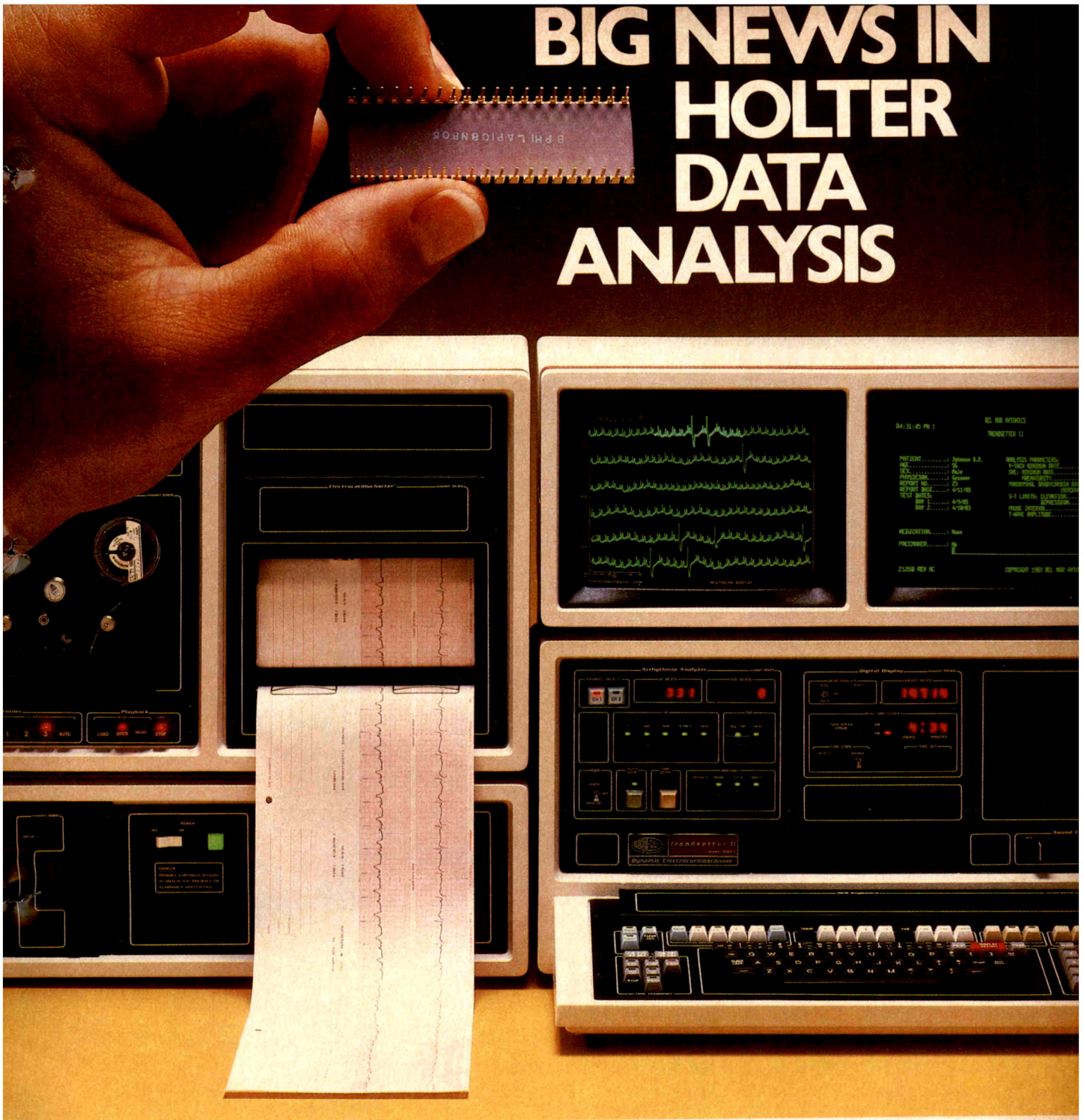

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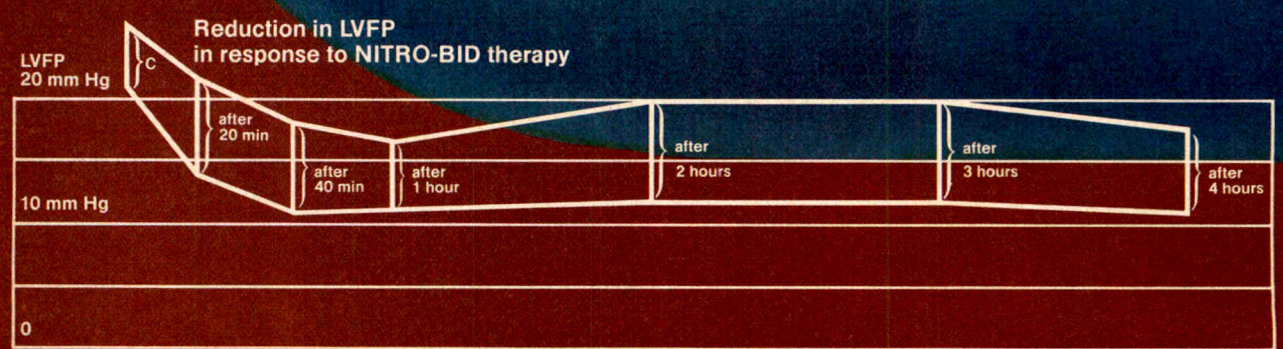

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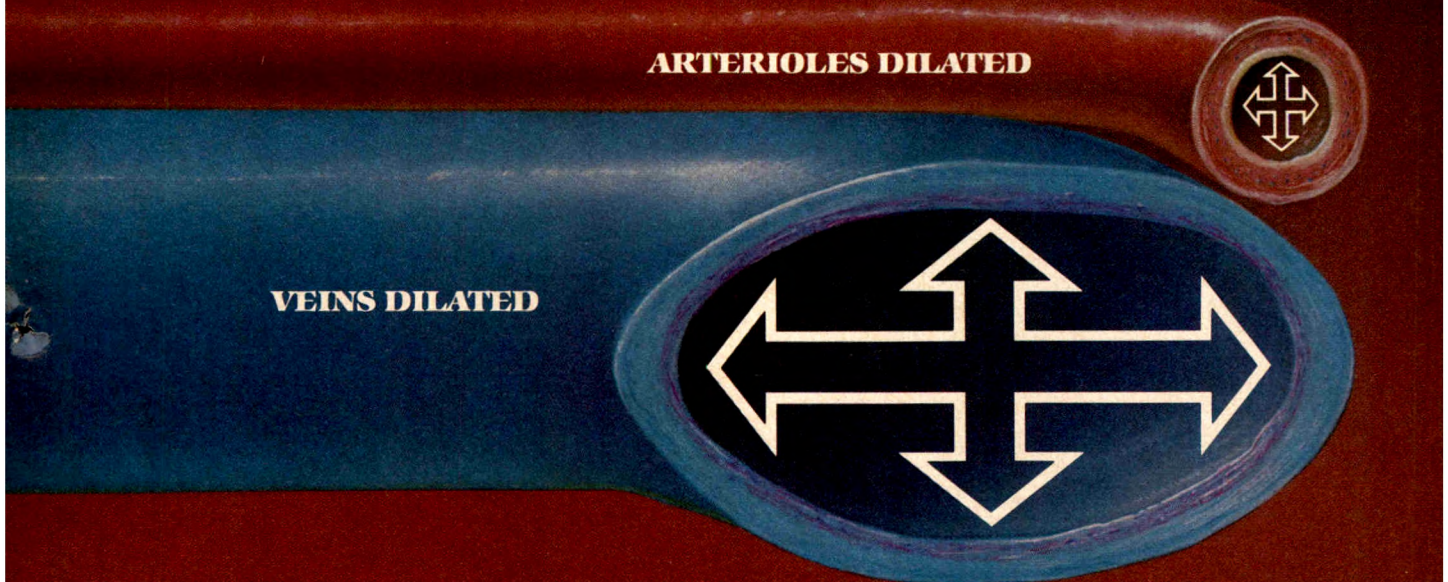

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PRECAUTIONS: Intraocular pressure may be increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug and cross-tolerance to other organic nitrites and nitrates may occur. If blurring of vision, dryness of mouth, or lack of benefit occurs, the drug should be discontinued.

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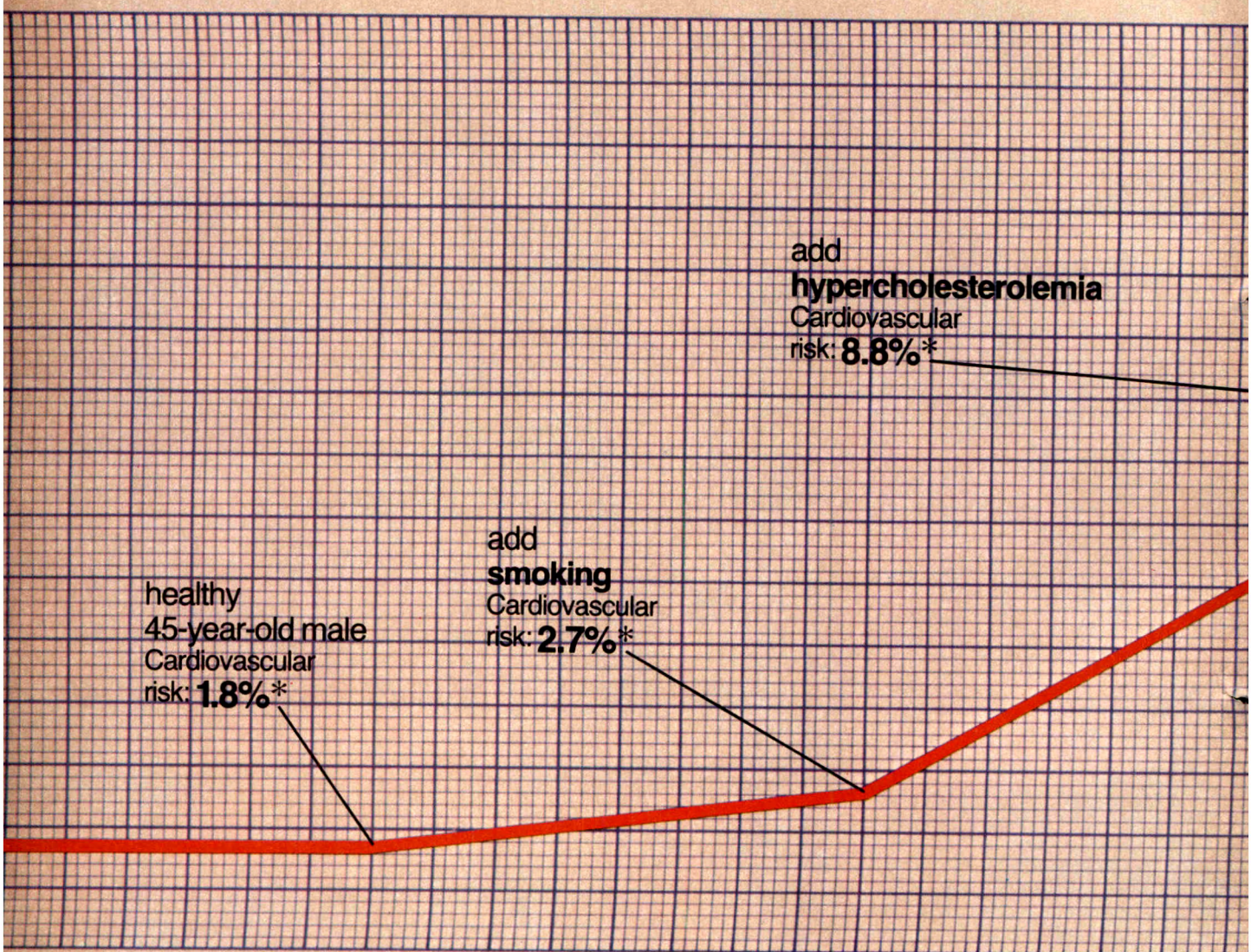

Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

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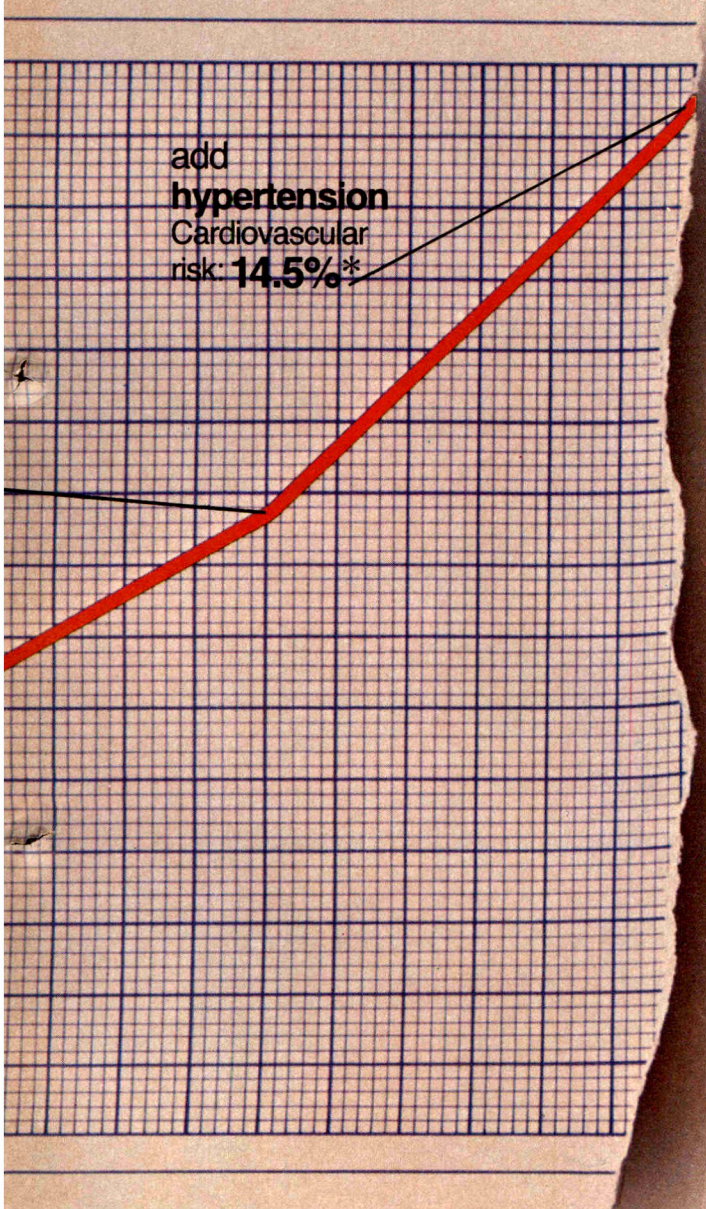

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WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.
If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.
Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.
ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
Initial Dose: 1 mg two or three times a day. (See Warnings.)
Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.
HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).
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Echocardiographic Evaluation of Porcine Bioprosthetic Valves: Experience With 309 Normal and 59 Dysfunctioning Valves

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To determine the clinical value of echocardiographic evaluation of porcine bioprosthetic valves, the findings in all patients who had porcine bioprosthetic valve replacement and adequate quality echocardiographic studies from 1978 to 1982 were analyzed. The study includes 309 normal and 59 dysfunctioning valves. Valve dysfunction resulted from spontaneous cusp degeneration in 39 (34 valve regurgitations, 5 stenoses), infective endocarditis in 12, paravalvular regurgitation in 5, regurgitation of redundant cusps, mitral valve thrombi, and aortic stent stenosis in 3 others. Echocardiographic findings were correlated with gross surgical pathologic or autopsy findings in 45 of the 59 dysfunctioning valves. Echocardiographic abnormalities were demonstrated in 41 of 59 (69%) dysfunctioning valves. A systolic mitral or diastolic aortic valve flutter was diagnostic of a regurgitant valve caused by a torn or unsupported cusp margin and was observed in 28 of 34 (82%) regurgitant valves with no false-positive studies. Echocardiographic cusp thickness of ≥3 mm correctly identified all regurgitant and stenotic valves with gross anatomic evidence of localized or generalized cusp thickening or calcific deposits. Echocardiographic valve abnormalities were observed in only 4 of 12 patients with infective endocarditis and in 1 of 5 with paravalvular regurgitation.

Thus, echocardiography provides important information regarding the function of porcine bioprosthetic valves and is of value in the decision to replace these valves, especially when dysfunction is due to spontaneous cuspal degeneration. Echocardiography is neither sensitive nor specific in patients with infective endocarditis and paravalvular regurgitation.

The stent-mounted, glutaraldehyde-fixed porcine bioprosthetic aortic valve has become one of the major prosthetic valves currently in use.[1–5] Although these valves have good hemodynamic features and a low rate of thromboembolism, dysfunction due to cusp degeneration can occur. The valve may also become infected, develop thrombus on its surface, or sustain nonleaflet structural changes.[6–10] Recognition of complications is important for prompt initiation of appropriate medical and surgical therapy. It is also important to establish normal function of the valve in the setting of changing symptoms or a deteriorating clinical state. Echocardiography has been beneficial in establishing normal as well as abnormal function of all prosthetic valves,[11–13] and particularly the porcine bioprosthesis.[14–23] This study reports our echocardiographic experience with normal and abnormal porcine bioprosthetic valves and provides information that may assist in differentiating the various forms of valve dysfunction.

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Methods

Of 424 echocardiographic studies of porcine bioprosthetic valves (Hancock and Carpentier-Edwards) performed in our laboratory between 1978 and 1982, 368 (89%) were technically adequate, as defined by the echocardiographic demonstration of ≥1 of the 3 cusps of the heterograft valve.

All M-mode echocardiographic studies were performed from the left parasternal approach using commercially available instruments. The valve cusps were differentiated from the echocardiographic reflective stents by recording their opening and closing motion. The cusps, once visualized, were expanded and slowly scanned for abnormal motion or flutter and records taken at 50 or 100 mm/s paper speed. The maximum thickness of the valve was measured from enlarged recordings in the closed position, that is, during systole in the mitral position and during diastole in the aortic position.

TABLE I Clinical Characteristics of Valve Dysfunction

	Valves (n)	Echocardiographic Valve Abnormalities	
		n	%
Spontaneous degeneration	39	33	85
Valvular regurgitation (34		28	82
Valvular stenosis (5)		5	100
Bacterial endocarditis	12	4	33
Paravalvular regurgitation	5	1	20
Redundant aortic valve	1	1	100
Aortic stent stenosis	1	1	100
Valve thrombus (probable)	1	1	100
Total	59	41	69

Great care was taken not to influence the valve thickness by using a high-gain or a low-reject setting, or both. Whenever possible, the initial diastolic slope and systolic excursion of the anterior stent of the mitral valve and the maximal systolic cusp opening and internal stent dimensions of the aortic valve were measured.[14,15]

Adequate-quality 2-dimensional (2-D) echocardiographic studies were also available for analysis in 79 normal and 38 dysfunctioning valves. All 2-D studies were evaluated in the parasternal long and short axis and, recently, apical 4-chamber views.

Results

During the 4 years of study, 309 of the 368 valves were adjudged normal clinically and echocardiographically. In this normal group, 203 valves were implanted in the mitral, 101 in the aortic, and 5 in the tricuspid location. The remaining 59 patients exhibited clinical deterioration or infection with valvular stenosis, regurgitation, or death resulting from valve dysfunction. In 41 (69%) of these, the valve abnormality was detected by echocardiography (Table I). In this abnormal group, 35 valves were implanted in the mitral, 22 in the aortic, and 2 in the tricuspid position.

Normal function: M-mode echocardiograms of normal porcine bioprosthetic valves in the aortic, tricuspid, and mitral position are shown in Figure 1. The systolic opening of the aortic valves ranged from 10 to 24 mm and the internal stent diameter from 15 to 25 mm. The range of the initial diastolic stent slope of the mitral valves was 4 to 33 mm/s and the systolic excursion of the anterior stent ranged from 5 to 15 mm/s. Fine fluttering motion of the normal open aortic cusps was often observed during systole. Fluttering of normal open mitral valve cusps during diastole was usually observed with aortic regurgitation or atrial fibrillation and flutter. Fluttering of the aortic, mitral, or tricuspid cusps in the closed or coapted position was never observed in a normally functioning valve. The echocardiographic features of the cusps are similar in both Hancock and Carpentier-Edwards valves. However, they can be differentiated from each other by 2-D study by their stent shape and configuration.

The average echocardiographically measured thickness of the porcine bioprosthetic valve in the closed position when implanted in a mitral position was 1.23 ± 0.12 mm for the mitral and 0.91 ± 0.07 mm for the aortic position. Valve thickness remained the same or increased only minimally during serial follow-up study except for 14 valves that became ≥3 mm thick.[23] In this latter group we observed a significant increase in the occurrence of valve dysfunction.[23] Progression of valve thickness is shown in Figure 2 in a patient with serial follow-up study.

Abnormal function: Fifty-nine instances of valvular dysfunction occurred (Table I); 39 were ascribed to spontaneous cusp degeneration, 12 to infective endocarditis, 5 to associated paravalvular regurgitation, and 1 each to regurgitation of redundant aortic cusps, mitral valve thrombus, and supravalvular aortic stenosis due to inward bending of the stents. Diagnostic echocardiographic abnormalities were observed in 69% of the patients. Valvular pathology was established within 1

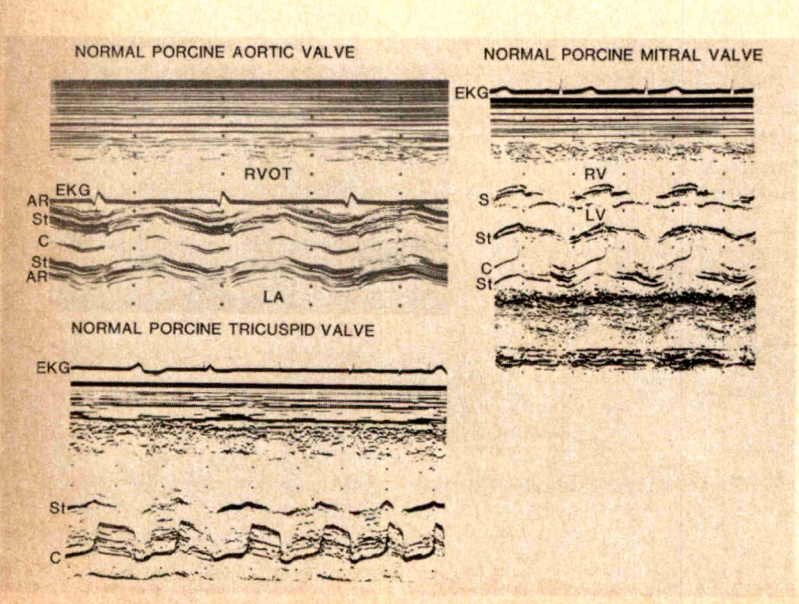

FIGURE 1. M-mode echocardiogram of a normal aortic, tricuspid, and mitral porcine bioprosthetic aortic valve. All valves are enlarged to demonstrate the cusps (C) which are thin. AR = aortic root; C = cusps; EKG = electrocardiogram; LA = left atrium; LV = left ventricle; RV = right ventricle; S = ventricular septum; St = stents; RVOT = right ventricular outflow tract.

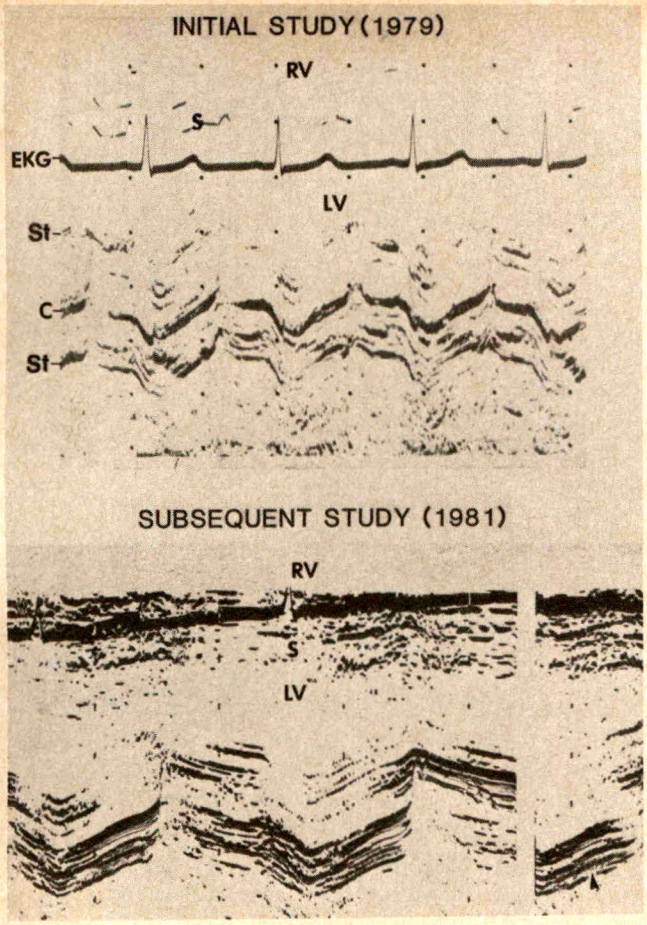

FIGURE 2. M-mode echocardiogram of porcine bioprosthetic mitral valve (magnified view). **Upper panel,** 1979; **lower panel,** 1981, at time of clinical dysfunction. Note progressive increase in cusp thickening and subtle high-frequency systolic fluttering (**arrow head**). Abbreviations are as in Figure 1.

month by cardiac catheterization (38 valves) and/or open heart surgery or autopsy (45 valves).

Spontaneous cusp degeneration: Spontaneous degeneration of the bioprosthesis occurred in 39 patients, 34 of whom had severe valve regurgitation and 5 had stenosis. Valve regurgitation is usually associated with a tear or perforation of a thickened and calcified cusp. Perforation and valve tears may also occur in valves that appeared to be of normal thickness on gross inspection. However, stenosis was always the result of thickening or calcification of the cusps, or both.

Of 34 patients with severe valve regurgitation, 28 developed rapidly progressive exertional dyspnea and 6 were minimally symptomatic and had detection by routine echocardiography. Two patients with stenotic aortic valves developed symptoms of angina, dyspnea, and near-syncope. All 3 patients with stenotic mitral valves had symptoms of progressive dyspnea.

The characteristics of echocardiographic abnormalities in spontaneous valve degeneration depend on whether the valves are predominantly stenotic or regurgitant. Echocardiographic valve abnormalities were observed in 85% of clinically significant dysfunctioning porcine bioprosthetic valves (Table II). All 5 stenotic valves produced abnormal echocardiograms, whereas valve regurgitation occurred with normal cusp echoes in 6 of 34 instances (18%).

Cusp degeneration causing regurgitation: Valve regurgitation was echocardiographically characterized by cusp fluttering, flail cusp motion, and increased cusp thickness. Cusp fluttering in the closed position of both aortic and mitral valves was distinctly abnormal. Diastolic fluttering of the aortic valve and systolic fluttering of the mitral valve in M-mode studies was diagnostic of porcine bioprosthetic valve regurgitation (Fig. 3 and 4). The findings were observed in 28 of 34 (82%) regurgitant valves with similar frequency in both the mitral and the aortic position. On inspection, these regurgitant valves had tears in 1 or more cusps. Because normal valves did not exhibit flutter in the closed position, this finding was 100% specific and of predictive value for regurgitant valves.

Diastolic fluttering of the open mitral and tricuspid valves can be normal. However, it was the only abnormality observed in 2 regurgitant mitral and 2 tricuspid valves. In 5 other regurgitant mitral valves, both diastolic and systolic fluttering were observed. When the valve cusps were poorly supported, flail motion and hyperflexion of parts of the disrupted aortic porcine valve cusps could be seen in the left ventricular outflow tract in diastole (Fig. 3). Portions of the flail mitral valve cusps were similarly observed in the left atrium during systole or left ventricular outflow tract during diastole (Fig. 4). This flail valve motion was particularly well appreciated in the 2-D mode study when the cusps were also thickened.

Echocardiographic cusp thickness of ≥3 mm was observed in 24 of 34 (70%) regurgitant valves. All such valves exhibited some localized or generalized cusp thickening or calcification on gross examination. In 6 valves with clinical evidence of significant valvular regurgitation, echocardiography was normal in 3 valves in the aortic position and 3 in the mitral. As increased valve thickness was also observed with 14 normal functioning valves, the predictive valve of this echocardiographic finding for regurgitant valves was only 63%.

Cusp degeneration causing stenosis: In 5 stenotic porcine valves, measurements of the valve thickness were always ≥3 mm. Aortic valves (Fig. 5) in 2 patients manifested reduced systolic cusp opening of 3 and 6 mm

TABLE II Clinical and Echocardiographic Characteristics of Spontaneous Valvular Degeneration

	Patients With Clinical Syndrome (n)	Echocardiographic Valve Abnormality	
		n	%
Valvular regurgitation			
Mitral	21	18	86
Aortic	11	8	73
Tricuspid	2	2	100
Valvular stenosis			
Mitral	3	3	100
Aortic	2	2	100
Total	39	33	85

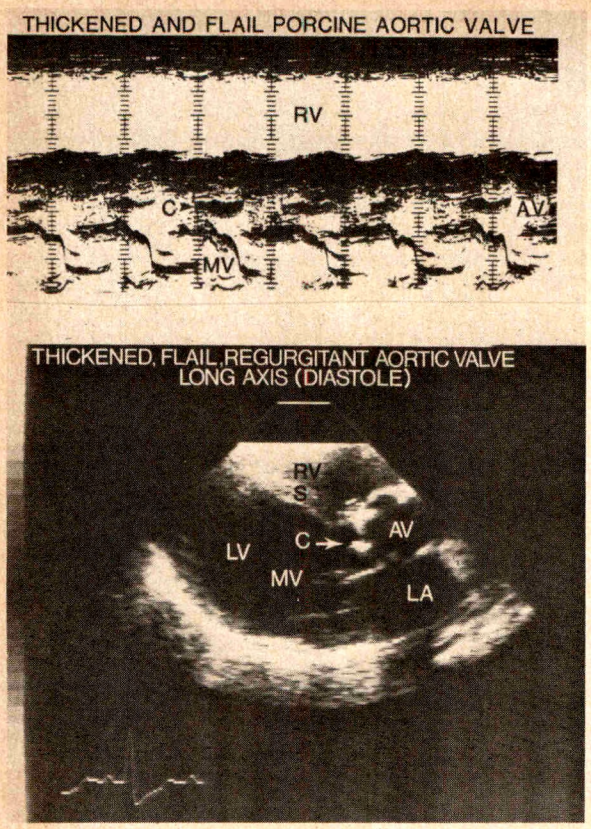

FIGURE 3. M-mode and 2-dimensional echocardiogram of a thickened, regurgitant, and flail porcine bioprosthetic aortic valve. **Upper panel,** note the thickened cusps (C) with diastolic flutter and prolapse into the left ventricular outflow tract. **Lower panel,** parasternal long-axis view of the valve during diastole. Note the thickened and flail cusps (C) in the left ventricular outflow tract. AV = aortic valve; MV = mitral valve; other abbreviations are as in Figure 1 in this and subsequent figures.

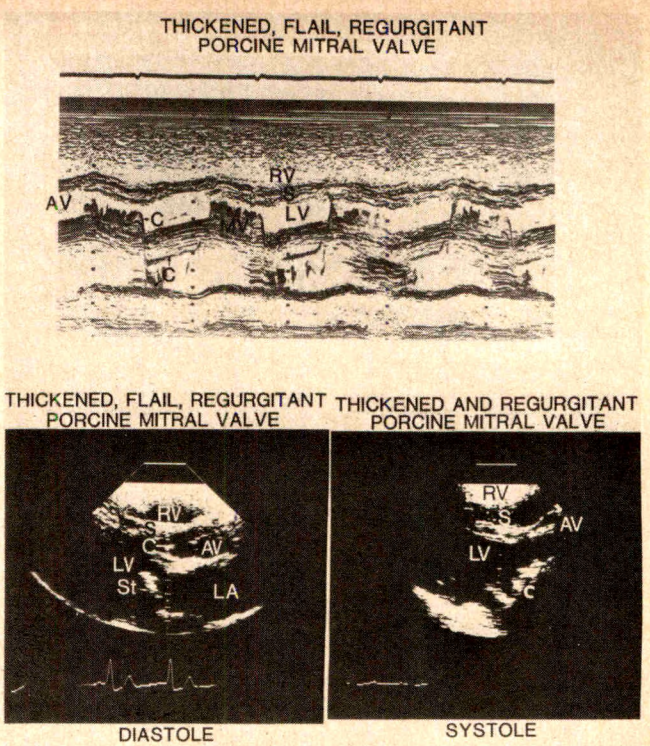

FIGURE 4. M-mode and 2-dimensional (2-D) echocardiogram of a thickened regurgitant and flail porcine bioprosthetic mitral valve (MV). **Upper panel,** note thickened cusps (C) with coarse diastolic and coarse and fine systolic fluttering (**arrows**). **Lower panel,** 2-D parasternal long-axis view during diastole and systole. Note the thickened cusp (C), which, during diastole, bends and hyperflexes anteriorly and toward the aortic valve (AV).

(normal 10 to 24). Although dense cusp echoes were demonstrated in all 3 stenotic mitral valves, the presence of reduced (<5 mm/s) initial diastolic stent slope motion was observed in only 1 instance.[9]

Infective endocarditis: The 12 patients with infective endocarditis presented with high fever, new murmurs, and positive blood cultures. Cusp echoes of ≥3 mm and a suggestion of valvular vegetations (Fig. 6) were observed in 4 of 12 patients by M-mode study and in 3 of the 6 studied by 2-D echocardiography. In 2 patients, no vegetations were seen despite their presence at surgery or autopsy.

Paravalvular regurgitation: Of 5 patients with this hemodynamic abnormality, 4 had normal studies. The only patient with an abnormal echocardiogram had a subanular aneurysm with marked displacement of the entire prosthesis into the left atrium (Fig. 7).

Mitral valve thrombus: One patient with apparent mitral valve thrombus was observed to have a marked, transient increase in cusp echoes (Fig. 8). This patient complained of shortness of breath and exhibited a diastolic murmur. These features, as well as increased cusp echoes, resolved after 1 week of intravenous heparin therapy. Although we cannot be absolutely certain, the clinical course and echocardiographic findings are highly suggestive of a thrombus on the porcine bioprosthetic valve.

Aortic insufficiency due to cusp redundancy: Occasionally the porcine bioprosthetic valve may not be structurally normal at the time of replacement. In 1 such patient, severe aortic regurgitation developed soon after aortic valve replacement. This patient had chaotic diastolic cusp fluttering. At surgery, the valve was intact, free of vegetations, and without a paravalvular leak. However, 1 aortic cusp was extremely redundant and poorly supported by the stent.

Supravalvular aortic stenosis due to inward bending of the stent: One patient had obstruction in the supravalvular area causing a loud systolic murmur, severe hemolytic anemia, and hemodynamic evidence of outflow obstruction.[10] M-mode study of this valve revealed normal cusps with a reduced internal diameter of the stent measuring 10 mm (normal >15 mm). Presence of marked inward bending of the stent with otherwise normal cusps was found at surgery.

Discussion

Normal functioning porcine bioprosthetic valves (Hancock or Carpentier-Edwards) have thin cusps and exhibit normal closing and opening during the cardiac

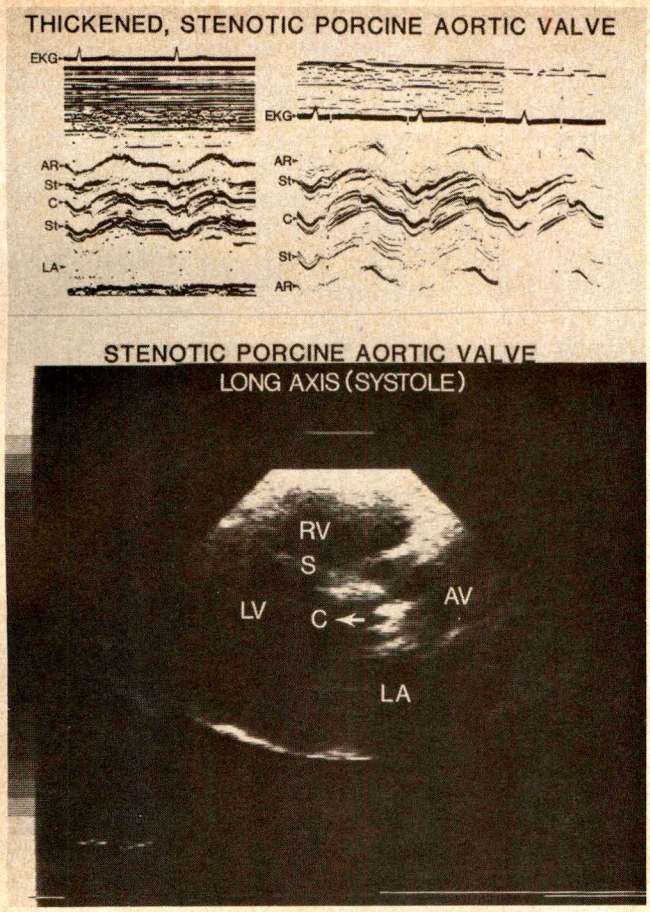

FIGURE 5. M-mode (**upper panel,** normal and magnified views) and 2-dimensional parasternal long-axis view (**lower panel**) echocardiogram of a thickened and stenotic porcine bioprosthetic aortic valve. Note the thickened cusp (C) with reduced systolic opening.

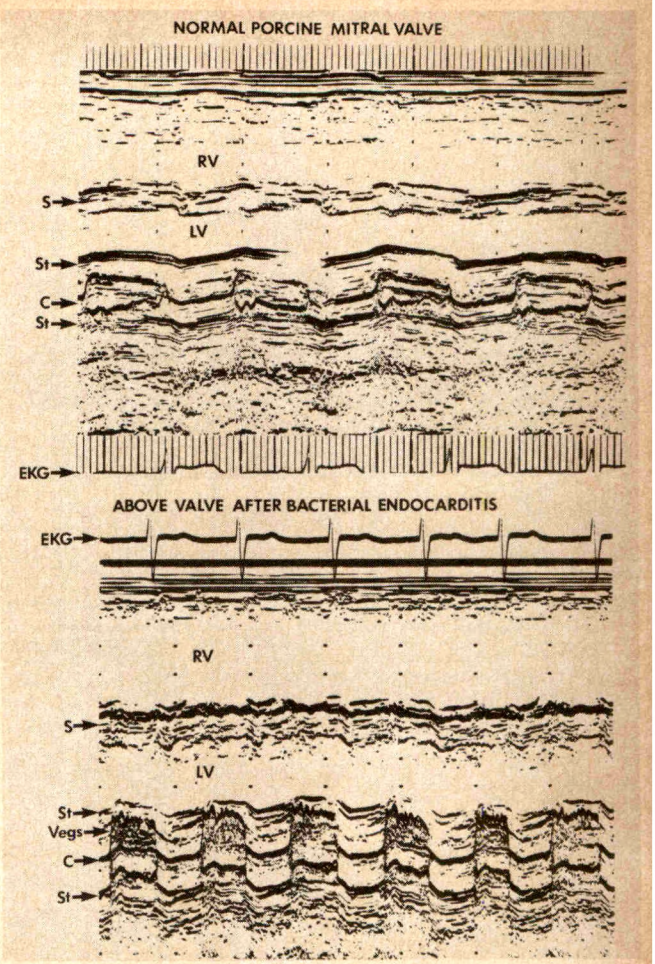

FIGURE 6. Upper panel, M-mode echocardiogram of patient with normal mitral porcine bioprosthetic valve. **Lower panel,** same valve 3 months later with vegetation (Vegs).

cycle. The gross pathology of degenerated porcine prosthetic valves usually reveals thickened and calcified cusps, with or without tears of the cusps.[24–26] However, tears of the cusps may occur without thickening or calcification. The presence of echocardiographic cusp fluttering of the closed valve indicates torn, nonsupported cusp tissue as a result of vibrations created at the margins of the tear. Similar fluttering has been observed with flail native valves and regurgitation associated with aortic homograft valves.[9,27] In our experience, fluttering of the mitral and aortic porcine valve in the closed position is always indicative and highly specific of regurgitation. On occasion, significant regurgitation may occur in the absence of demonstrable fluttering. It is usually associated with small valve tears, and the narrow ultrasonic beam may have missed the involved valve segment. Enlarging and slow scanning of the entire valve circumference while recording at fast paper speed will reduce the likelihood of missing this subtle finding. Fluttering of the mitral and tricuspid valves, when open in diastole, can be observed in both regurgitant and normal valves. In the normal functioning mitral valve, diastolic fluttering was observed particularly in the presence of aortic regurgitation and atrial fibrillation

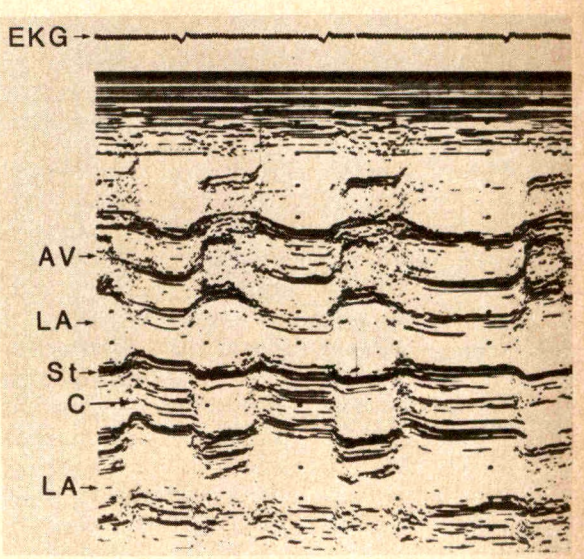

FIGURE 7. M-mode echocardiogram of a mitral porcine bioprosthetic valve with severe perivalvular regurgitation and displacement of both stent and cusp echoes in the left atrium.

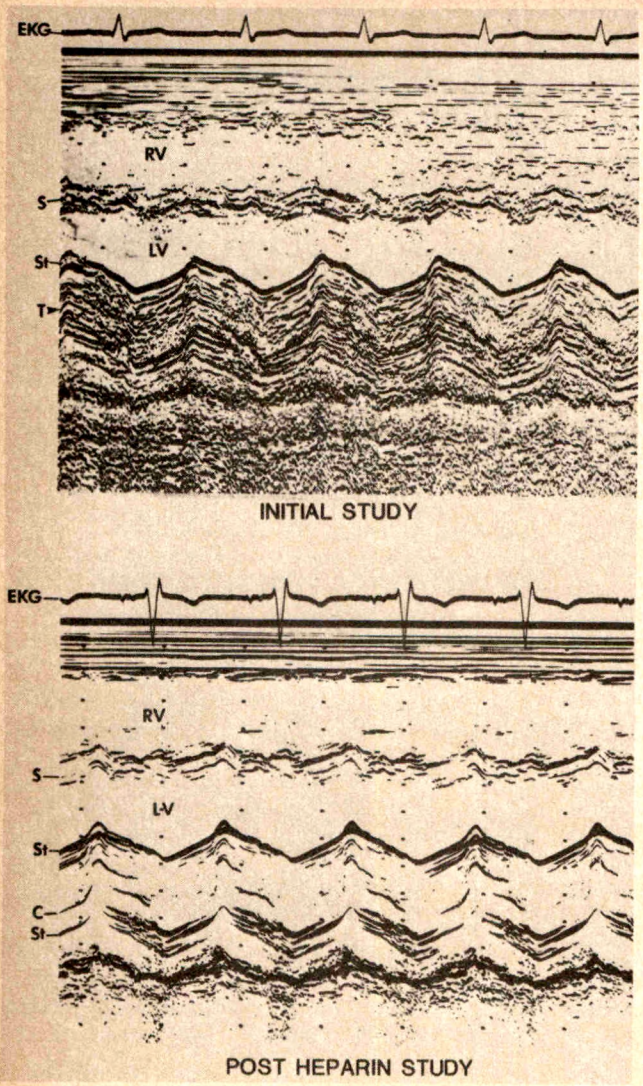

FIGURE 8. Upper panel, M-mode echocardiogram of a probable thrombus on porcine bioprosthetic mitral valve. Note the dense echoes of the thrombus (T) in the region of the mitral valve. **Lower panel,** same valve after probable thrombolysis. Note normal cusp (C) echoes.

and has been reported with paravalvular regurgitation.[18]

Cusp thickening is a sensitive and early indication of valve degeneration. Our experience indicates that cusp thickness ≥3 mm in asymptomatic patients usually represents subclinical valve degeneration and frequently leads to clinical signs of valve dysfunction.[23] Because symptoms of valve dysfunction may take many months to develop, we do not advise replacement of thickened valves until the patient becomes symptomatic. However, cusp thickening of ≥3 mm is not highly specific for spontaneous valve degeneration, because some thickening can be observed with valve vegetations or thrombus. It may also be an artifact created by a very high gain setting.

The echocardiographic characteristics of stenotic aortic porcine prosthetic valves are similar to those of native aortic valve stenosis. In porcine bioprosthetic mitral valves, the echocardiographic findings were similar to those reported by Horowitz et al[9] for stenotic mitral homograft valves except that reduced initial diastolic stent slope was present in only 1 of the 3 patients. Furthermore, a reduced diastolic stent slope (<5 mm/s) was also observed with normally functioning mitral valve prostheses when left ventricular compliance was decreased. As all stenotic valves have echocardiographic cusp thickness ≥3 mm, it has been our practice to measure transvalvular pressure gradients in any patient who develops dyspnea in association with echocardiographic evidence of increased valve thickness.

In the evaluation of porcine bioprosthetic valve endocarditis, both M-mode and 2-D echocardiography were neither sensitive nor specific. Shaggy, fluttering echoes characteristic of native valve vegetations[28] were observed in only 1 patient. Similar shaggy echoes were also observed in patients who had primary valve degeneration and regurgitant valves. Schapira et al[17] reported the superiority of 2-D over M-mode echocardiography in the evaluation of porcine bioprosthetic valve vegetations and masses, but we could not support this opinion.

Because severe paravalvular regurgitation is usually due to technical factors at the valve ring and not to cusp abnormalities, it is not surprising that the valve echoes of all but 1 patient with this entity were normal. Echocardiographic features of paravalvular mitral regurgitation, previously reported, increased initial diastolic slope of the anterior stent (>33 mm/s) and systolic excursion of the anterior cusps (>10 mm), and fine diastolic fluttering of the cusps[14,18] was not observed in any of our patients.

Increased cusp echoes in our patient with probable mitral valve thrombus was similar to those reported by Bloch et al.[14] Reduced diastolic excursion of the leaflet as reported by Horowitz et al[9] could not be appreciated in our patient because of echoes from the overlying thrombus. Chandraratna and San Pedro[15] reported an increase in the thickness of the posterior stent and a reduction of the space between the stent and the aortic root to be diagnostic of an aortic porcine bioprosthetic valve thrombus. We have observed this finding with normally functioning valves.

Structural abnormalities of the valve occur, albeit rarely. Our 1 patient with a redundant aortic cusp had diastolic fluttering echoes similar to those reported with regurgitant native myxomatous aortic valves.[29] Valvular aortic stenosis due to inward bending of the stent should be considered in any patient with an echocardiographically determined internal aortic stent diameter <15 mm.

We did not find that either 2-D or M-mode echocardiography provided a unique advantage. Valve fluttering is better identified in the M-mode and flail valve motion by 2-D studies. Each technique was important and provided a different visualtion modality. Bioprosthetic valve dysfunction is thus best identified using both techniques.

The echocardiogram can provide critical information regarding the function of porcine bioprosthetic valves and can substantially assist in the decision to replace

these valves in a symptomatic patient. Because patients with valvular heart disease often have periods of cardiac decompensation unrelated to valve dysfunction, careful echocardiographic evaluation may prevent unnecessary valve replacement in functionally normal valves and expedite surgery in those patients with significantly dysfunctioning valves.

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Abnormal Cardiovascular Regulation in the Mitral Valve Prolapse Syndrome

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Studies of patients with mitral valve prolapse syndrome have suggested autonomic nervous system dysfunction, but a precise definition of mechanisms is lacking. We measured supine and standing heart rate, blood pressure, cardiac output, oxygen consumption, plasma catecholamines, and blood volume in 23 symptomatic women with both echocardiographic and phonographic signs of MVP and in 17 normal control subjects. An analysis of the results revealed 2 distinct subgroups of patients: those with normal heart rates but increased vasoconstriction (Group I, n = 10) and those with orthostatic tachycardia (Group II, n = 13). Group II patients had heart rates at rest supine of 97 ± 3 compared with 79 ± 2 in Group I patients and 78 ± 8 in control subjects. Estimated total blood volumes were lowest in Group I patients, intermediate in Group II patients, and highest in control subjects ($p < 0.05$). Other measurements at rest supine were similar in patients and controls. After standing for 5 minutes, patients had a higher mean plasma epinephrine value, diastolic blood pressure (81 ± 2 versus 74 ± 3 mm Hg, $p < 0.05$), and peripheral resistance (1,878 ± 114 versus 1,414 ± 92, dynes s cm^{-5}, $p < 0.01$), wider arteriovenous oxygen difference (6.7 ± 0.4 versus 5.3 ± 0.5 vol%), and lower stroke volume index (26 ± 2 versus 33 ± 2 ml/m^2, $p < 0.01$) than did the control subjects. Cardiac output was normal in Group II patients but reduced in Group I patients, who demonstrated marked vasoconstriction. No patient had evidence of a "hyperkinetic" circulatory state. A cycle of decreased forward stroke volume, vasoconstriction, and blood volume contraction appears to be present in at least some symptomatic patients with MVP.

Reports from our laboratory[1,2] and others[3–5] have documented the presence of autonomic nervous system dysfunction in some patients with the mitral valve prolapse (MVP) syndrome, but a precise definition of the regulatory abnormalities has not been presented. Coghlan et al[3] reported that some patients appeared to have excessive vagal tone and responsiveness. Boudoulas et al[5] recently suggested that patients with MVP are hyperadrenergic, with increased beta-adrenergic tone and responsiveness. Our previous work provided no evidence for increased beta-adrenergic activity, but rather, suggested that alpha-adrenergic hyperactivity was present. A common feature in all of these reports is that the conclusions were based partly on the response to orthostatic stress produced by head-up tilt,[3] standing,[4,5] or lower body negative pressure.[1] Because of differences in findings, we carried out a second set of studies in which the hemodynamic and neuroendocrine responses of patients with MVP to orthostatic stress were analyzed.

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Methods

Patients: The patient group consisted of 23 women aged 36 ± 2 years (mean age ± standard error) (range 21 to 60). Patient characteristics are shown in Table I. All patients had presented for medical care because of symptoms commonly associated with MVP such as chest pain, palpitations, easy fatigability, and near-syncope, often in response to orthostatic

stress. None had clinical evidence of significant mitral regurgitation, coronary artery disease, hypertension, diabetes mellitus, or alcoholism. None of the subjects in this study group met Diagnostic Standards Manual-III criteria for panic disorder. Neuroactive medications were discontinued at least 1 week before study. MVP was diagnosed by 2-dimensional (2-D) echocardiography and phonocardiography.[1] Criteria for echocardiographic diagnosis included prolapse of 1 or both leaflets behind an imaginary line through the mitral anulus in either the apical 4-chamber or the parasternal long-axis views. All subjects had persistent auscultatory findings including isolated single or multiple nonejection clicks with or without the murmur of mitral regurgitation. No subject with "silent" or "echo-only" MVP was included. Family studies in more than half the subjects confirmed the familial nature of the disorder.

Control subjects for the hemodynamic studies were 17 women, mean age 27 ± 1 years. All were healthy nonsmokers, taking no cardio- or neuroactive medications. They were employees of the University of Texas Health Science Center or the Parkland Memorial Hospital in Dallas, Texas. Most were sedentary and none participated regularly in athletics.

Procedures: Heart rate was measured by the electrocardiogram and displayed digitally on a beat-to-beat basis (Quinton Cardiotachometer, model 511). Indirect arterial blood pressure was measured semiautomatically with a device that records simultaneous cuff pressure and Korotkov sounds (Narco Bio-Systems Electro-Sphygmomanometer, PE-300). Cardiac output was measured with an acetylene rebreathing technique previously validated in our laboratory. The coefficient of variation when compared with simultaneous indocyanine green cardiac outputs was 4.3% over a range of 4 to 19 liters/min.[6] Oxygen consumption and cardiac output were simultaneously measured to calculate arteriovenous oxygen differences. Plasma catecholamines were measured by a radioenzymatic technique.[7] Plasma volume was measured by standard dilution techniques using either human serum albumin tagged with iodine-125 (RISA) or Evans blue dye.[8,9] Iodine-125 was used in 4 of 23 patients and 3 of 17 control subjects. Measurement of plasma volume by both RISA and Evans blue methods in 7 subjects revealed a nonsignificant mean difference of 183 ± 104 ml (RISA values being higher). Total blood volume was estimated from measurement of plasma volume and peripheral venous hematocrit corrected for trapped plasma and the difference between central and peripheral venous hematocrit.[10,11]

Protocol: The study was approved by the local Human Research Review Committee. Each subject gave informed written consent before study. Although most patients and subjects had participated in similar hemodynamic studies previously, care was taken to familiarize each person with the laboratory procedures and equipment. This familiarization was always accomplished a day before the study was performed. Testing of patients and control subjects was performed concurrently.

On the first day of study, a small needle was placed in an arm vein and kept open with heparinized saline solution. Baseline cardiac output, heart rate, and blood pressure were measured. After at least 20 minutes of supine rest, a venous blood sample was drawn for plasma catecholamine determination. Hemodynamic measurements were then repeated. The subject then stood quietly for 5 minutes, after which catecholamine sampling and hemodynamic measurements were again repeated.

Measurement of plasma volume was performed on a second day with the subject at rest supine for approximately 1 hour. Hematocrit was determined on simultaneously obtained peripheral blood samples.

TABLE I Subject Characteristics

	Mitral Valve Prolapse		Normal Control Subjects
	Group I (HR <100)	Group II (HR ≥100)	
n	10	13	17
Age (yr)*	39.0 ± 4.1	33.5 ± 2.4	26.9 ± 1.0
Height (cm)	167.7 ± 2.0	167.6 ± 2.2	167.8 ± 1.8
Weight (kg)	56.8 ± 2.3	55.7 ± 2.6	58.8 ± 1.6
BSA (m^2)	1.64 ± 0.03	1.62 ± 0.04	1.66 ± 0.03

* $p < 0.01$.
BSA = body surface area; HR = heart rate.

Statistical analysis was performed with the use of the Statistical Analysis Systems programs.[12] Because an initial analysis of the results revealed the presence of 2 hemodynamically distinct subsets of patients, an analysis of variance was used to test for differences between the control subjects, the patients with normal supine and standing heart rates (Group I), and those with tachycardia when standing (Group II). Results are expressed as the mean ± standard error of the mean. Differences were statistically significant to a level of probability of $p < 0.05$.

Results

Supine: Cardiac and stroke volume indexes, calculated arteriovenous oxygen differences, and total peripheral resistance for patients and control subjects were not significantly different (Fig. 1). Mean arterial pressure was higher in the patients. Heart rate was increased only in the patients with standing tachycardia (Group II). Mean plasma norepinephrine levels were similar, but plasma epinephrine levels were significantly higher in patients compared with the control subjects (31 ± 5.7 versus 11 ± 3.7 pg/ml, $p < 0.01$). These values, although at the lower limits of detectability, correlated significantly with heart rate ($p < 0.001$) and systolic blood pressure ($p < 0.001$).

Standing: As expected, cardiac indexes decreased significantly on standing in both patients and control subjects; Group I patients had lower mean cardiac indexes than did Group II patients or control subjects. Both patient groups had a higher mean diastolic arterial blood pressure (81 ± 3, 79 ± 2, and 72 ± 2 mm Hg, $p < 0.05$, respectively), with a subnormal stroke volume index ($p < 0.05$). Plasma norepinephrine levels increased in all groups. Again, the intergroup differences were not statistically significant, but several individual patients had very large increases on standing, and there was a downward progression from Group II patients with tachycardia to normal control subjects (Fig. 2). Plasma epinephrine levels were not significantly different from values obtained in the supine position. Measurements of heart rate, blood pressure, and stroke volume also showed large interindividual differences among the patients. Total peripheral resistance (Fig. 1) was significantly higher in Group I patients, with no tachycardia; Group II patients had intermediate values, whereas the controls had the lowest. An identical pattern was seen for calculated arteriovenous oxygen difference (6.90 ± 0.60, 6.77 ± 0.39, and 5.70 ± 0.26 vol%, respectively).

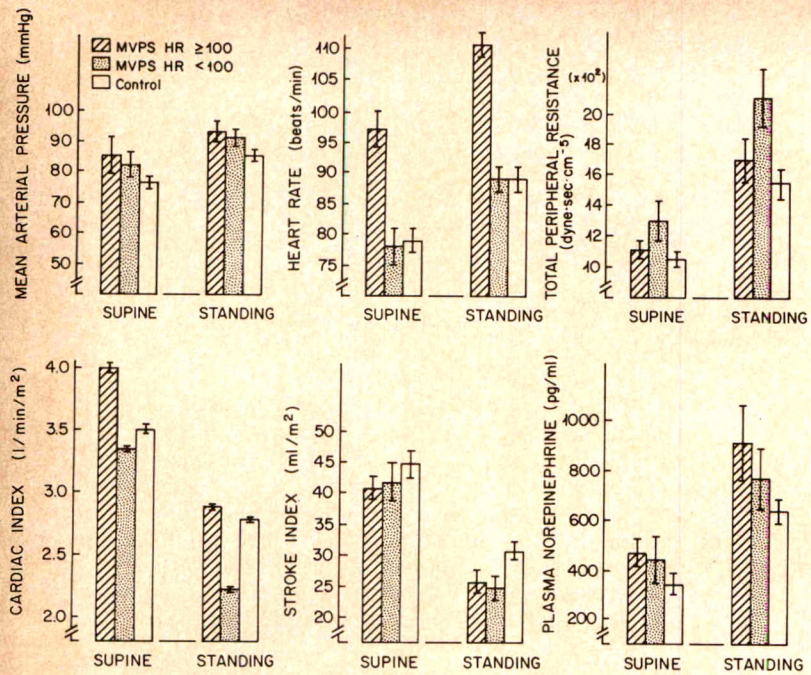

FIGURE 1. Hemodynamic and neuroendocrine measurements in patients with normal heart rates (Group I), patients with orthostatic tachycardia (Group II), and normal control subjects. MVPS = mitral valve prolapse syndrome; HR = heart rate. Values are mean ± 1 standard error.

Plasma volume: Overall, patients had a significantly higher hematocrit (40.3 ± 0.9 versus 37.6 ± 0.6%, $p < 0.02$) and lower plasma volume, both in absolute terms (2,836 ± 82 versus 3,222 ± 123 ml, $p < 0.01$) and when corrected for height (17.0 ± 0.5 versus 19.2 ± 0.7 ml/cm, $p < 0.01$). There were similar differences in absolute blood volume and when correction was made for height or body surface area.[13] Group I patients, who had the highest total peripheral resistance, had the lowest blood volumes, 4,012 ± 100 ml; Group II patients had intermediate values, 4,406 ± 133 ml, and control subjects had 4,798 ± 231 ml ($p < 0.05$).

Discussion

The present study demonstrates that a subgroup of patients with MVP, characterized by the presence of symptoms and both echocardiographic and auscultatory/phonographic signs of prolapse, have an abnormal response to orthostatic stress. They develop excessive vasoconstriction and, in some cases, tachycardia, and maintain a higher mean arterial blood pressure (standing) than do normal control subjects. By themselves, heart rate and blood pressure data suggest a hyperkinetic response, but when examined relative to the overall hemodynamic response, a different pattern emerges. Stroke volume tends to be slightly lower in the supine position, and on standing is significantly lower in both groups of patients with MVP. In Group II patients, there is tachycardia on standing, and cardiac output is maintained at normal levels. In Group I patients, the response is actually hypokinetic, as reflected in the tendency toward wider calculated arteriovenous oxygen differences in the patient group in the upright position. Group I patients, when standing, seem to compensate for decreased forward stroke volume by vasoconstriction. However, if the patients had a purely compensatory response, their blood pressure should have been slightly lower than normal, rather than significantly higher than the control group values.

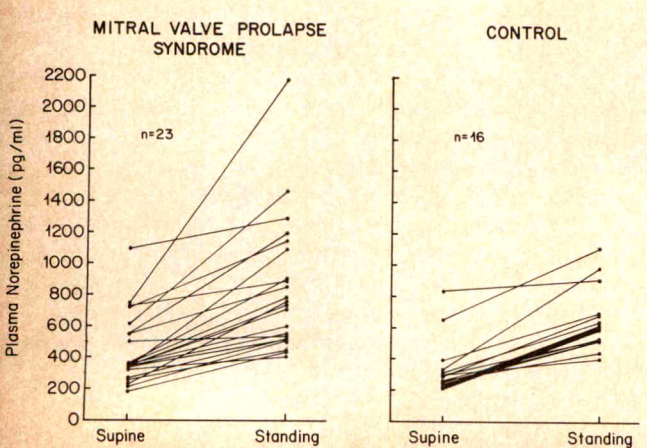

FIGURE 2. Supine and standing plasma norepinephrine values for each patient and each normal control subject.

The hemodynamic heterogeneity of the patients makes interpretation of the average norepinephrine responses difficult. Other investigators have found small but significant differences between patients with MVP and control subjects.[4,5] Our patients also tended to have higher plasma norepinephrine levels, but interindividual variations were large and the intergroup differences did not reach statistical significance (Fig. 2). Whether or not a group difference will be recorded is determined in large part by the number of patients in the study who have orthostatic intolerance and tachycardia as major complaints. The finding that certain patients with MVP have tachycardia and increased norepinephrine levels on standing does not constitute proof of beta-adrenergic hyperactivity, that is, an ab-

normal hemodynamic state primarily attributable to abnormal levels of beta-adrenergic stimulation. Patients with the higher norepinephrine levels also had the higher heart rates which served to maintain cardiac output to a more normal degree than did the "normal" heart rate. The 13 patients with the highest norepinephrine levels and standing heart rates over 100 beats/min (Group II patients) had a mean cardiac index of 2.9 ± 0.2 liters/min/m^2, whereas the patients (Group I) with standing heart rates under 100 had a significantly lower cardiac index (2.3 ± 0.2 liters/min/m^2). Other investigators[4,5] noted an apparently inappropriate response in patients with MVP on standing, but cardiac output measurements were not performed. The lack of cardiac output data led to the conclusion that a hyperkinetic state was present, whereas the present study suggests that the heart rate response is reasonably appropriate considering the stimulus, that is, an orthostatic blood volume shift producing a low forward stroke volume. The increase in arterial pressure above normal levels during orthostatic stress despite a substantial decrease in cardiac output has been noted previously[1] and suggests an abnormal alpha-adrenergic responsiveness with appropriate beta-adrenergic activity. The alpha-adrenergic hyperactivity in the upright position may eventually lead to a chronic state of vasoconstriction and increased plasma catecholamine levels. The fact that orthostatic intolerance in some patients with pheochromocytoma provides some support for the hypothesis that a neuroendocrine postural response that is beneficial on a short-term basis may contribute to a chronic state of orthostatic intolerance.[14] Similar changes may also be seen in subjects rendered hypovolemic by prolonged bed rest or space travel.[15]

A possible link between excessive vasoconstriction, hypovolemia, and MVP is presented in Figure 3. A large postural reduction in forward stroke volume leads to marked vasoconstriction and increased catecholamine release. This chronic vasoconstriction leads to hypovolemia, which produces an even greater reduction in forward stroke volume in the presence of MVP. A vicious cycle is established. Substantial mitral regurgitation is not a prerequisite. The increasing volume contained by the ballooning leaflets with decreasing ventricular size may produce, for any given reduction in left ventricular filling pressure, an exaggerated decrease in resting fiber length, fiber shortening, and forward stroke volume. Our preliminary finding of a marked reduction in left ventricular end-diastolic volume in patients with MVP with upright rest or exercise supports the concept that decreased ventricular filling in the upright position is a prominent feature in the pathophysiologic mechanisms of this syndrome.[2] Semiquantitative measurement of leg volume changes during orthostatic stress produced by lower body negative pressure showed that patients with MVP did not have excessive blood pooling in their legs,[1] suggesting that the decrease in total blood volume is an important component of orthostatic intolerance in patients with MVP.

Such a decrease in blood volume might also be at least a partial explanation for the recent findings of Devereux et al,[16] who noted significantly lower sitting blood

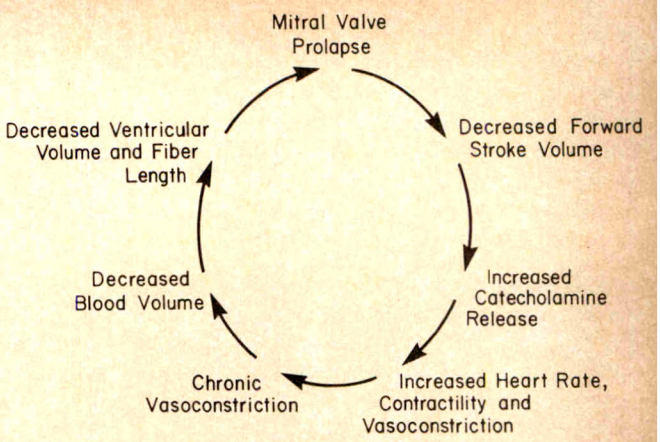

FIGURE 3. A proposed pathophysiology of orthostatic intolerance in symptomatic patients with mitral valve prolapse (MVP). A large myxomatous mitral valve would clearly have a facilitative role, but it is not necessary in order to have MVP or MVP symptoms related to orthostatic intolerance.

pressure in a large number of patients with MVP. The presence of an increased frequency of palpitations in Devereux's MVP patients[17] as well as ours[1] may reflect the presence of orthostatic intolerance as recently reported by Santos et al.[18] Such patients are commonly seen and, in addition to palpitations, give a history of near-syncope or syncope, but an ambulatory electrocardiographic recording often shows only sinus tachycardia. Unless a diary of patient activity is available, the extent of tachycardia without exertion or excitement is often not appreciated.

The existence of parasympathetic and alpha-adrenergic dysfunction in some patients with MVP suggests a primary abnormality affecting the autonomic nervous system. Two-dimensional echocardiographic studies in our patients, who all had auscultatory signs of prolapse, revealed a wide spectrum of mitral leaflet size and degree of valvular prolapse. These factors appear to be unrelated to the degree of symptoms present. Jeresaty[19] noted a similar lack of correlation between symptoms and the degree of prolapse, which suggests that at most, the prolapsing valve plays a facilitating role in producing these orthostatic symptoms, but that it is not their primary cause. This subgroup of patients with orthostatic intolerance clearly has a syndrome consisting of distinctive anthropometric characteristics,[20] autonomic dysfunction,[1–5] and myxomatous degeneration of the mitral valve. Whether MVP is causally related to the symptoms of the patients in the present study is not known. Additionally, the presence of chronic vasoconstriction, hypovolemia, and orthostatic and exercise intolerance in similar patients without MVP (personal observation) suggests that the pathophysiologic mechanisms are by no means specific to MVP, but rather, explain the symptoms found in a variety of cardiac disorders. Data from other investigators provide some support for the hypothesis that there are other subgroups of patients with anatomically normal mitral valves, but with symptoms and signs of the MVP syndrome because of autonomic dysfunction including an increased inotropic state with reduced left ventric-

ular volume. Wooley[21] reported the clinical similarities between patients with MVP and hyperkinetic syndromes, such as the vasoregulatory asthenia described by Holmgren et al[22] and the hyperkinetic heart syndrome reported by Gorlin.[23] Whether some of these patients classified as hyperkinetic actually have midsystolic clicks, murmurs, and echocardiographic evidence of MVP is not known.

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Noncardiovascular Findings Associated With Heart Disease in the Idiopathic Hypereosinophilic Syndrome

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Heart disease characterized by endomyocardial fibrosis is one of the major causes of morbidity and mortality in the idiopathic hypereosinophilic syndrome. From our series of 50 patients with idiopathic hypereosinophilia, we defined the noncardiovascular characteristics that distinguish patients at risk of developing endomyocardial fibrosis from those who remain free of heart disease. These groups did not differ with respect to the extent of eosinophilia or the duration of disease. Patients with clinically overt heart disease were more likely ($p < 0.05$) to be male and HLA-Bw44 positive and have splenomegaly, thrombocytopenia, elevated serum levels of vitamin B_{12}, and hypogranular or vacuolated eosinophils and abnormal early myeloid precursors in the peripheral blood. These idiopathic hypereosinophilic patients with heart disease were also more likely to have fibrosis and decreased megakaryocytes in the bone marrow. In contrast, those who remained free of heart disease tended to be female and have angioedema, hypergammaglobulinemia, elevated serum levels of immunoglobulin E (IgE), and circulating immune complexes.

Therefore, in the idiopathic hypereosinophilic syndrome, male patients with a myeloproliferative type disorder and the HLA-Bw44 haplotype were at a much increased risk for the development of endomyocardial fibrosis. However, those patients with a hypersensitivity-like illness and angioedema who were female did not develop heart disease. Appreciation of this relative degree of risk for the major complication of the idiopathic hypereosinophilic syndrome should prove useful in the early identification and appropriate treatment of patients in whom endomyocardial fibrosis might develop.

The endocardial disease associated with idiopathic eosinophilia was first appreciated by Löffler[1] in 1936. Since then, numerous reports and small series of patients have firmly established the association of these findings.[2–6] Indeed, cardiovascular disease has been recognized as the major cause of morbidity and mortality in patients with idiopathic eosinophilia.[6–8] The pathophysiologic mechanism that relates endomyocardial fibrosis to idiopathic hypereosinophilia is not known, although some patients with idiopathic hypereosinophilia and heart disease have morphologic changes in their peripheral blood eosinophils.[9]

In our experience not all patients with idiopathic hypereosinophilia develop clinical heart disease. This study was performed to discover the noncardiovascular findings that may distinguish the patients who develop heart disease from those who remain free of cardiovascular complications.

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Methods

Patients: The 50 patients included in this study were admitted to the National Institutes of Health Clinical Center under a National Institutes of Allergy and Infectious Diseases protocol. Patients were followed 2 to 14 years, although some have had eosinophilia for >20 years. Only those patients who satisfied the diagnostic criteria for the idiopathic hypereosinophilic syndrome were included in the study.[6] These criteria include (1) unexplained eosinophilia ≥6 months, (2) organ system involvement (any organ system except the skin alone is acceptable), and (3) the inability to establish an alternative diagnosis despite exhaustive evaluation.

The first available peripheral smears and bone marrows from each patient were read and scored blindly according to previously described criteria.[10] In addition, criteria were established to assess eosinophil morphologic characteristics. Eosinophils were scored as hypogranular if <50% of the area of the cellular cytoplasm on smear contained granules. Likewise, eosinophils that contained 10 or more vacuoles were scored as vacuolated.

Studies of eosinophil morphology showed that the determination of vacuolation and hypogranularity was not changed by storage at room temperature for up to 6 hours, by blood collection by vacutainer (EDTA), fingerstick or syringe, nor

TABLE I Patient Groups in the Idiopathic Hypereosinophilic Syndrome According to Cardiac Involvement: 50 Patients

	n	%	Total
Clinically overt cardiac involvement		42	21
Progressive valvular disease	16/21		
Deterioration of pump function	17/21		
Multiple emboli	8/21		
Subclinical cardiac involvement		12	
A. Increased septum or free wall thickness	4/6		
B. Increased density of the posterior mitral leaflet	3/6		
C. Ventricular filling defect	0		
Other cardiac disease		6	3
No evidence of cardiac disease		40	20

by using stained smears versus unstained smears evaluated by phase microscopy. Normal eosinophils did not become hypogranular or vacuolated, and the degree of hypogranularity and vacuolization of the abnormal eosinophils did not progress.

Classification of patients: Patients were assigned to 1 of 4 groups. Group I consisted of patients with overt cardiovascular disease as defined by the presence of either progressive valvular heart disease, congestive heart failure, or ≥3 embolic events to different arterial sites. Group II included patients with echocardiographic (M-mode or 2-dimensional) or electrocardiographic abnormalities consistent with idiopathic eosinophilia,[7–11] but without clinically overt heart disease. Group III included patients who had heart disease with a cause unrelated to idiopathic eosinophilia. Group IV patients had no heart disease.

Statistical analysis: The 2-tailed Student *t* test was applied to apparent differences in the anti-log of the log mean of quantitative determinations between groups. Fisher's exact test was used to compare the prevalence of characteristics between subpopulations. Survival data were compared by the Wilcoxon test. Differences were considered significant when the null hypothesis was rejected with >95% confidence.

Results

Of the 50 patients studied, 21 (42%) developed overt clinical heart disease (group I). Precordial murmurs that became louder were present in 16, mitral regurgitation

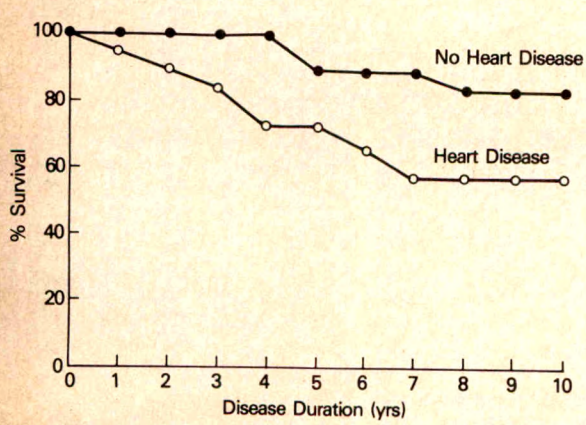

FIGURE 1. The survival of patients with overt heart disease (O) (group I) compared with that in patients who remain free of heart disease (●) (group IV).

TABLE II Comparison of Patient Groups

	Group I Heart Disease (n = 21)	Group IV No Heart Disease (n = 20)
Eosinophilia (cells/μl)*	20,700	19,000
Duration of disease (yr)	5.0	5.3
Average NIH follow-up (yr)	3.2	2.9
Average age at presentation (yr)	36	27

* Extent of eosinophilia at presentation.

in 15 of the 16. Otherwise, unexplained congestive heart failure occurred in 17 of these 21 patients and multiple emboli in 8 (Table I).

Six of the 50 patients had electrocardiographic or echocardiographic abnormalities in the absence of any evidence of overt clinical heart disease (group II). Four of these had left ventricular or free wall thickening on M-mode echocardiography, 3 had abnormal motion and thickening of the posterior mitral leaflet on 2-dimensional echocardiography, and 4 had nonspecific changes on electrocardiography (Table I).

Three patients had heart disease from other causes (group III). One had long-standing aortic regurgitation; 1 had a bicuspid and calcified aortic valve by echocardiography; and 1 had an acute myocardial infarction and angina pectoris. Groups II and III contained too few patients to yield meaningful results and, therefore, have been omitted from the following analysis.

Twenty patients had no evidence of heart disease (group IV). Direct comparison of the patients with heart disease (group I) with those patients who remained free of clinical heart disease (group IV) revealed no significant differences ($p > 0.1$) with respect to the extent of eosinophilia at presentation, the duration of disease from onset, the average follow-up at the National Institutes of Health, nor the average age at presentation (Table II). However, survival was longer in patients with no heart disease (Fig. 1).

Except for the finding of splenomegaly and for the 6 patients who had overt heart disease at presentation, initial examination was not helpful in discriminating patients at risk for the development of heart disease. Of the 21 patients with heart disease, 19 had splenomegaly at presentation or developed it during follow-up; only 5 of the 20 patients who remained free of heart disease had splenomegaly ($p \leq 0.005$). Of these 5 patients, 4 had an apparent underlying cause for an association with splenomegaly such as generalized lymphadenopathy (in 3 patients) and Budd-Chiari syndrome (1 patient).

Clinical laboratory studies revealed substantial differences between patient groups. Those patients who remained free of heart disease had elevated serum immune complexes, IgE, and Ig (IgG, IgM, or IgA) as shown in Table III. Only 2 of 15 group I patients had elevated immune complexes, 3 of 15 had elevated IgE, and only 1 of 15 had both. Group I patients were also more likely to have thrombocytopenia, elevated serum B_{12}, and HLA-Bw44 (Table IV). Other clinical laboratory studies, such as white blood cell count, degree of eosinophilia, abnormal leukocyte alkaline phosphatase,

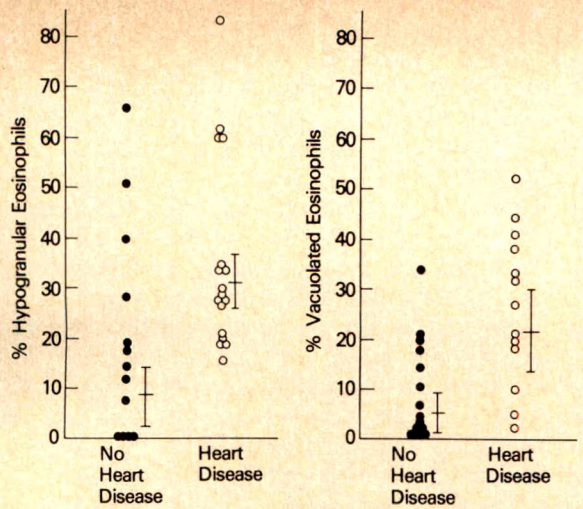

FIGURE 2. The proportion of hypogranular or vacoulated eosinophils at presentation was greater in the patients with heart disease (group I).

and frequency of anemia, were not significantly different between the 2 groups.

To develop the capacity to predict which patients were at risk for the development of heart disease, the earliest available morphologic material was reviewed (see Materials and Methods) and compared with the later clinical experience. The temporal sequence of splenomegaly and clinically detectable heart disease also was determined in each relevant case. An average of 32 ± 5% of the peripheral blood eosinophils were hypogranular in the patients who later developed heart disease (group I), whereas only 8 ± 6.5% were in group IV (Fig. 2). Vacuolated eosinophils were present in an average of 21 ± 8% of the peripheral blood eosinophils from group I and 3.8 ± 2.0% in group IV. The first available pretreatment platelet counts were substantially different, with an average of 168,000 ± 14,200 platelets/ml in group I and 414,000 ± 35,000 platelets/ml in group IV ($p < 0.001$). Abnormal erythrocyte morphology, myeloblasts, metamyelocytes, and myeloid dyspoiesis were more frequently found in the peripheral blood of the patients assigned to the group with overt clinical heart disease (Table V). Increased cellularity, fibrosis, and decreased megakaryocytes were more frequently found in the bone marrow at presentation in the patients with overt heart disease (group I).

In 8 of the 21 patients in group I it was possible to determine the order of appearance of splenomegaly and heart disease. In 6 of these 8, the splenomegaly preceded the heart disease, and in these patients an average of 10 ± 3 months (range 2 to 72) elapsed between the appreciation of splenomegaly and the onset of overt clinical heart disease. In 1 patient clinical heart disease clearly preceded splenomegaly by 27 months, and in 1 patient splenomegaly has not occurred 24 months after the onset of overt clinical heart disease. Thus, those patients with splenomegaly should be more carefully observed for the later development of heart disease.

The 2 women who developed heart disease were unusual. The first had severe bronchospasm and developed a dilated cardiomyopathy in conjunction with the eosinophilia. She was HLA-Bw44 positive but did not have splenomegaly or other characteristics of a myelo-

TABLE III Characteristics of the Patients Who Remained Free of Heart Disease

	Group I Heart Disease (n = 21)	Group IV No Heart Disease (n = 20)	Level of Significance (p)
Female	2 (10%)	9 (45%)	0.014
Angioedema	0	6 (30%)	0.009
Hypergammaglobulinema*	4 (19%)	12 (60%)	0.022
IgE (IU/ml)	23 ± 12 (15)†	430 ± 200 (14)	0.05
C1q binding (%)	6.6 ± 2.0 (15)	17 ± 5 (12)	0.05
Response to prednisone	3 (20%)	12 (80%)	0.003

* Elevated IgM, IgG, or IgA.
† Presented as the anti-log of the log mean ± standard error (n).

TABLE IV Characteristics That Discriminate Patients With Heart Disease

	Group I Heart Disease (n = 21)		Group IV No Heart Disease (n = 20)		Level of Significance (p)
	n	%	n	%	
Splenomegaly*	19	90	5	25	0.005
Thrombocytopenia	9	43	1	5	0.009
Vitamin B_{12} (pg/ml)	2100 ± 400		300 ± 150		0.01
HLA-Bw44	9	75	2	20	0.03

* Determined, when available, by liver-spleen scan (^{99}Tc sulphur colloid) or, alternatively, by the presence of a palpable spleen tip.
† Less than 135,000 platelets/μl at presentation.

TABLE V Morphologic Findings in Peripheral Blood and Bone Marrow at Initial Presentation

	Group I Heart Disease (n = 21)		Group IV No Heart Disease (n = 20)		Level of Significance (p)
	n	%	n	%	
Peripheral smear					
Abnormal erythrocyte morphology	12/18	67	6	30	0.048
Myeloblasts	5	24	0		0.048
Myelocytes or metamyelocytes	9	43	0		0.001
Myeloid dyspoiesis	10/16	62	3/15	20	0.029
Basophilia	11	52	7/21	33	>0.3
Bone marrow					
Increased cellularity	16/20	80	7/13	54	>0.2
Fibrosis	8/12	67	0/9		0.005
Decreased megakaryocytes	12/20	60	2/12	17	0.027
Basophilia	6/15	40	1/10	10	>0.1
Myeloid dyspoiesis	8/16	50	2/13	15	>0.1
Increased immature forms	3/16	19	0/13		>0.2
Percentage eosinophils	39 ± 6	16*	28 ± 8	13	>0.2

* Presented as the anti-log of the log mean ± standard error (n).

proliferative disorder. The second had a more typically myeloproliferative disease with splenomegaly and of advanced bone marrow disease. She was the only patient to have hypogranular and vacuolated eosinophils in the bone marrow as well as in the peripheral blood. However, this patient did not have the HLA-Bw44 haplotype.

Discussion

This analysis of a large population of patients with the idiopathic hypereosinophilic syndrome defines 2 patterns of clinical illness with respect to the development of heart disease. In one pattern, heart disease is accompanied by characteristics of a primary myeloproliferative type disease. These patients have splenomegaly, thrombocytopenia, and elevated serum vitamin B_{12}. They are more likely to have marrow fibrosis, immature myeloid forms, myeloid dyspoiesis, as well as abnormal eosinophil morphology in their peripheral blood.

Patients who have remained free of heart disease have characteristics of a more allergic or hypersensitivity process. They tend to have elevated Ig, especially IgE, and elevated levels of circulating immune complexes. In addition, all of the patients with angioedema are in this group.

Indeed, Löffler's original patients with this syndrome had splenomegaly along with their eosinophilia and cardiac involvement.[1] Particular attention was not focused on this association of splenomegaly with eosinophilia and heart disease until Shepard et al[12] pointed out the coincidence of these findings in their patients. Moreover, as we have shown herein, splenomegaly can predict the subsequent occurrence of overt clinical heart disease.

Other discriminating characteristics, in addition to splenomegaly, suggest a myeloproliferative syndrome in the patients who develop heart disease. The B_{12}-binding protein transcobalamin I is elevated in the myeloproliferative disorders and has been shown to be elevated in 1 patient with idiopathic hypereosinophilia. In addition, transcobalamin I has been found in eosinophils as well as neutrophils.[12,14] Except for an increased incidence of HLA-Bw44 and the sex ratio difference, the noncardiac associations that discriminate patients with heart disease from the remainder are all commonly recognized characteristics of myeloproliferative disorders.

Patients with HLA-Bw44 and idiopathic hypereosinophilia have an almost 4-fold increase in the risk of developing heart disease (Table III). The Bw44 haplotype was split from HLA-B12, which has been positively associated with follicular lymphoma, acute lymphoblastic leukemia, acute appendicitis, steroid responsiveness in nephrotic syndrome, and alopecia areata, and negatively associated with Buerger's disease and psoriasis vulgaris.[15] Perhaps the recently observed decreased responsiveness of lymphocytes from HLA-B12 donors to prostaglandin E_2 and histamine[16] is an important clue for these unexpected associations.

Our data establish the impression of earlier workers that those patients with idiopathic hypereosinophilia who develop heart disease have a poorer prognosis when compared with that of patients who remain free of heart disease[6,17,18] (Fig. 1). In addition, the improvement in morbidity and lifestyle of patients treated early in the course of their heart disease with appropriate medical and surgical management[19] emphasizes the importance of identifying predictive variables for and against the development of heart disease.

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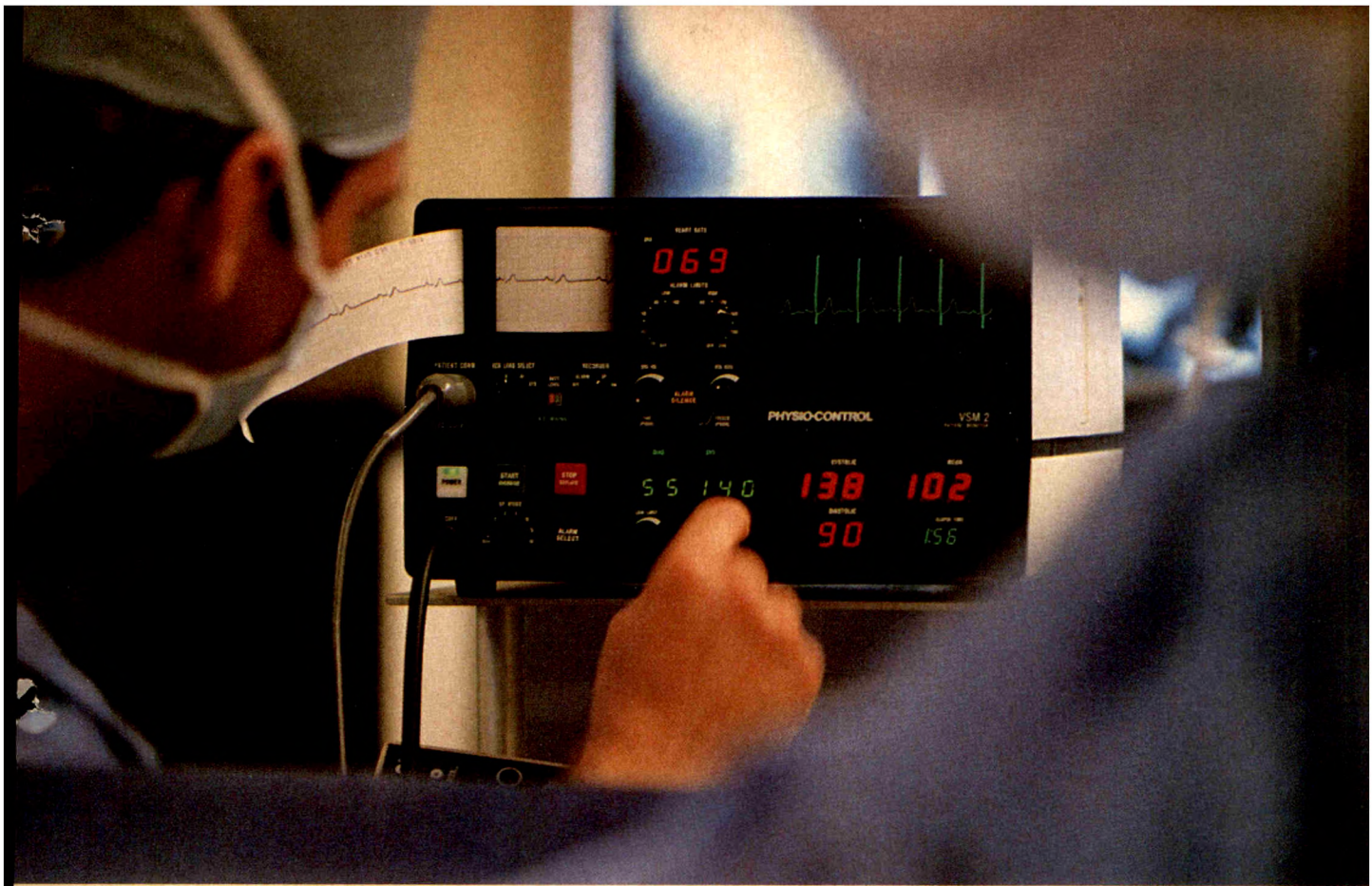

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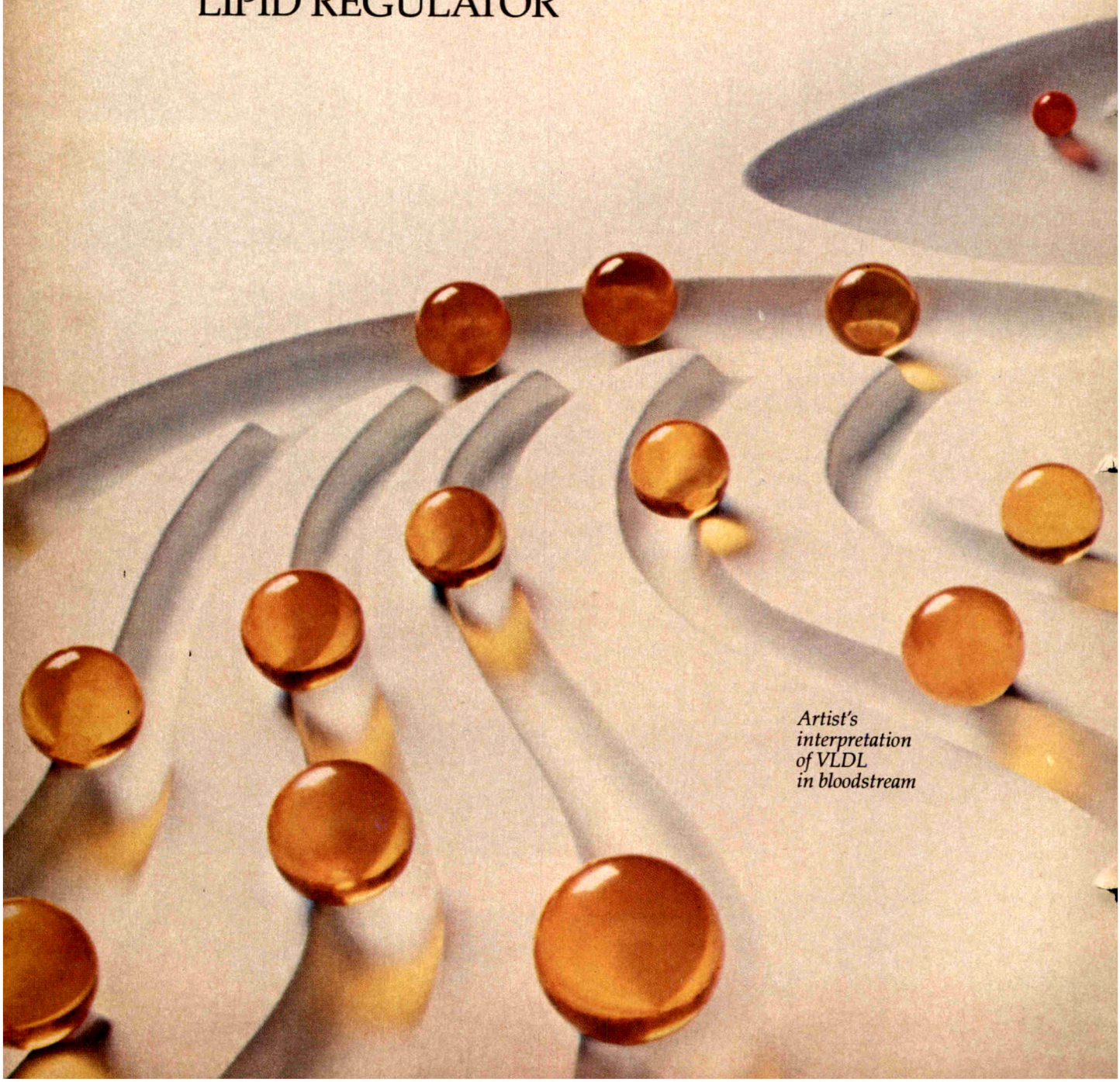
MORE THAN A LIPID-LOWERING AGENT— A TWO-WAY LIPID REGULATOR

Favorably regulates the balance of lipid fractions in certain dyslipidemias:

1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent, cholesterol-rich LDL (very-low- and low-density lipoproteins implicated in dyslipidemia)

2/May also RAISE serum levels of HDL (high-density lipoproteins believed to transport cholesterol to the liver for catabolism and excretion)

LOPID is indicated for treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.

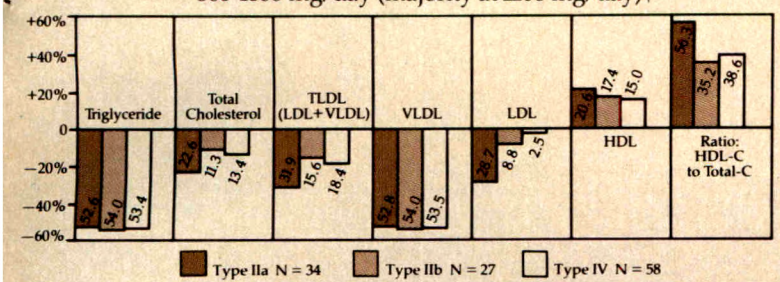


Artist's interpretation of VLDL in bloodstream

Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†



*Visit every 4 weeks during long-term use of LOPID.
†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

Convenient BID dosage

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

Reference:
1. Data on file, Medical Affairs Dept, Parke-Davis.

Artist's interpretation of HDL in bloodstream

LOPID® 300-mg capsules
(gemfibrozil)

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LOPID®
(gemfibrozil)
A LIPID REGULATOR

LOPID® (gemfibrozil) Capsules

Before prescribing, please see full prescribing information.
A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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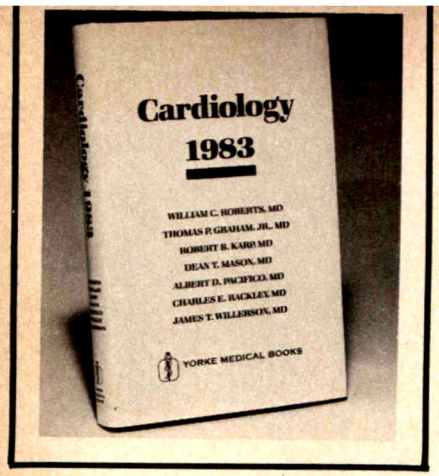

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Cardiology 1983

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Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

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Two-Dimensional Echocardiographic Assessment of Surgically Closed Ventricular Septal Defect

JOSE L. ANDRADE, MD, WALTER SERINO, MD, MARC de LEVAL, MD, and JANE SOMERVILLE, MD

One hundred twenty patients operated on for closure of a ventricular septal defect (VSD) had postoperative assessment by 2-dimensional echocardiography. The presence of persistent "drop-out" between ventricular septum (VS) and the periphery of the "patch" was considered a sign of detachment and residual shunt. Echocardiographic findings of intact VS or residual VSD were correlated with angiographic findings in 30 patients and with clinical signs in 90 patients. Minute shunts with increased flow ratios <1.5:1 were occasionally missed. Persistent small drop-out was sometimes wrongly diagnosed as residual shunt when the patch was in an angled position and in the early postoperative weeks when peripatch edema of the VS suggested drop-out. Thus, 2-dimensional echocardiography is a reliable method for assessing significant persistent ventricular shunts and intact VS after surgical closure of a VSD.

After surgical closure of a ventricular septal defect (VSD), it is important to know that the defect has been completely closed, since this will influence symptoms and long-term advice.[1,2] When clinical signs suggest that a defect persists, invasive investigation has been used to determine the residual dynamics and anatomy. Contrast M-mode echocardiography has been useful in the immediate postoperative period to demonstrate residual shunt or adequate closure.[3] Now that real-time 2-dimensional (2-D) echocardiography is available for assessing the anatomy of the ventricular septum (VS),[4,5] it is an ideal method for assessment of the surgically closed VSD. The present study was undertaken in 120 patients who had been operated on for closure of VSD to assess the reliability of 2-D echocardiography in detecting persistent defects and complete surgical closure.

Methods

Patients: Between June 1981 and November 1982, 120 consecutive patients who had previous surgery for closure of VSD were assessed with 2-D echocardiography at the National Heart Hospital. Fifty patients had isolated VSD, and in 70 the VSD was part of a more complex cardiac malformation, such as Fallot's tetralogy (33), pulmonary atresia (14), atrioventricular defect (7), double-outlet right ventricle (5), transposition of the great arteries (4), corrected transposition of the great arteries (4), and truncus arteriosus (3).

An Advanced Technology Laboratory mechanical sector scanner MK300C using a 3.0-MHz transducer was used. Technically satisfactory visualization of the VS and the "patch," which appeared as an area of highly reflective echoes,[6] was required. Records were made from parasternal (4-chamber, long- and short-axis), apical (4-chamber), and subcostal (4-chamber and short-axis) planes.[7] The terminology used is as described by Capelli et al,[5] in which VSDs are classified as subvalvular, subdivided according to the valve they lie beneath (inlet, subtricuspid, subaortic, subpulmonary, and doubly committed subarterial), or muscular, subdivided according to where they are in the muscular ventricular septum (apical, central, and outlet).

Residual interventricular shunts were diagnosed on 2-D echocardiography when a partial detachment of the patch from the VS with systolic shift into the right ventricle was seen, with persistent echocardiographic drop-out between VS and the periphery of the patch. Based on the spatial orientation of the VS, the areas of drop-out were referred to as anterior, posterior, inferior (caudal), or superior (cephalic) (Fig. 1).

The rest of the VS was carefully profiled to look for a residual VSD which might have been missed at operation. Evidence of chamber enlargement was not used as a sign of persistent VSD, although it was noted. In the 120 patients the

From the Paediatric & Adolescent Unit, National Heart Hospital, London, England. This study was supported in part by a research fellowship from Squibb Medical Systems, London, England. Manuscript received January 31, 1983; revised manuscript received April 18, 1983, accepted April 21, 1983.

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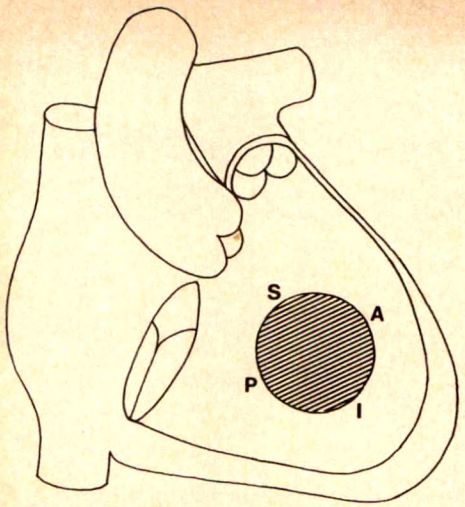

FIGURE 1. Diagram showing the main sites of a patch detachment. A = anterior; I = interior; P = posterior; S = superior.

site of the patches and the presence or absence of a residual VSD on 2-D echocardiography were interpreted by 1 of us, without previous knowledge of the clinical signs or of the postoperative angiographic findings (Table I).

Ninety patients had no invasive postoperative investigation, and 30 had cardiac catheterization with left ventricular angiography. The patients were divided according to the presence or absence of 2-D echocardiographic features of residual VSD, and these findings were correlated with physical signs and angiographic findings (Table II).

Results

Diagnosis of residual VSD by 2-D echocardiography: Thirty-four patients were considered to have a persistent VSD from the appearances on 2-D echocardiography. Sixteen of these had cardiac catheterization and angiography, and a residual ventricular shunt was shown in 13. In 3 patients, no evidence of interventricular shunts was found. Twelve of the 13 patients with angiographic confirmation of residual shunt have had reoperation, and the position of detachment was confirmed to be at the site suggested by 2-D echocardiography. No separate missed VSDs were found. Two-dimensional echocardiography was repeated after reoperation and confirmed an intact VS. In another patient, a reversed right-to-left shunt was found and reoperation was contraindicated. Contrast echocardiography in this patient had confirmed the right-to-left shunt through the reopened defect (Fig. 2). Eighteen patients in whom 2-D echocardiography suggested the presence of a persistent VSD had no invasive investigation. Physical signs of residual shunt were present in 14 of them and absent in 4. In these 4 patients 2-D echocardiography was performed within the first postoperative week.

The basic anatomy of the VSD in those in whom it was echocardiographically found to be opened was as follows:

Inlet: Four patients had a residual VSD in this area. The residual defect appeared in 4-chamber view as a detachment between the posteroinferior part of the patch and the crest of the septum (Fig. 3). This was confirmed angiographically and at reoperation in 2 patients.

Subtricuspid: Nine patients with patched subtricuspid VSD had detachment in the inferoposterior part of the VS seen in 4-chamber view (Fig. 4). This was confirmed by angiography and reoperation in 3.

Subaortic: Sixteen patients with persistent defect had had patching of a large subaortic VSD. In 11, the long-axis view of the left ventricle showed a discontinuity between the anteroinferior part of the patch and the crest of the VS (Fig. 5A). This was confirmed by angiography in 3 and at reoperation in 2. In 5 patients the drop-out appeared anterosuperiorly between the patch and the anterior wall of the aorta (Fig. 5B). This was confirmed by angiography and at reoperation in 2.

TABLE I Site of the Patches and Presence or Absence of Residual Ventricular Septal Defect (VSD)

2-D Echocardiographic Findings	Inlet Area	Subtricuspid Area	Subaortic Area	Muscular Area	Subpulmonary Area	Doubly Committed
Residual VSD	4	9	16	5	...	...
Intact VS	7	15	47	9	3	5

VS = ventricular septum.

TABLE II Echocardiographic, Clinical, and Angiographic Findings

2-D Echocardiographic Findings	Cases (n)	Angiographic Group*		Clinical Group†	
		Residual VSD	No VSD	Signs of Residual VSD	No Signs of Residual VSD
Residual VSD	34	13	3	14	4
Intact VS	86	2	12	3	69

* Patients with postoperative invasive investigation.
† Patients without invasive investigation.
VS = ventricular septum; VSD = ventricular septal defect.

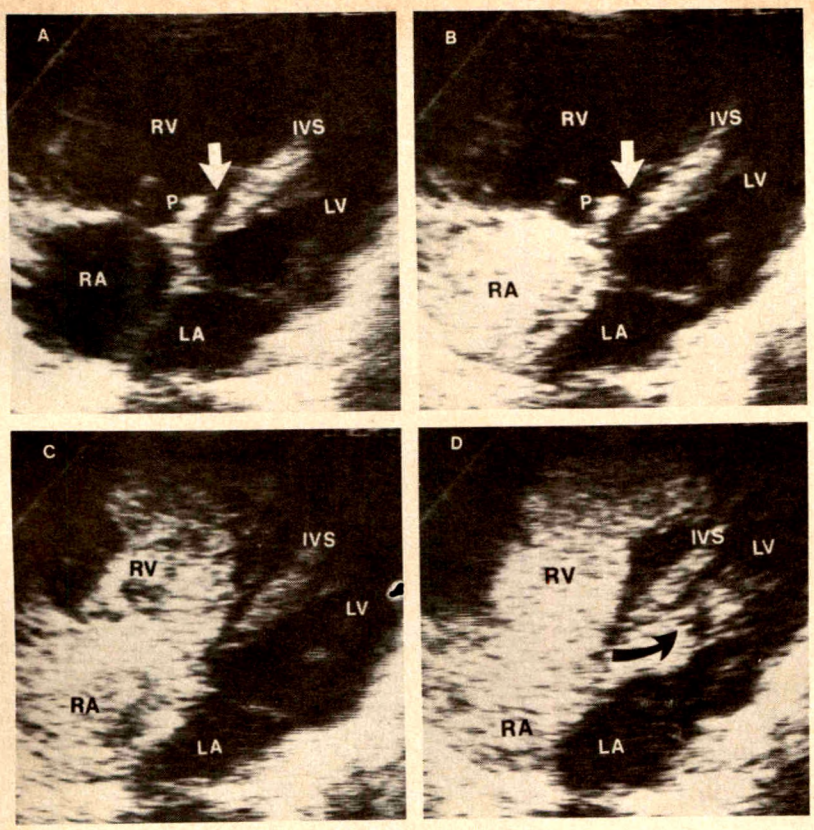

FIGURE 2. Contrast 2-dimensional echocardiograms from a patient with a patched subaortic VSD and clinical and angiographic signs of an irreversible right-to-left ventricular shunt. **A,** parasternal 4-chamber view before the contrast injection showing a persistent inferoposterior VSD (**white arrow**). **B,** contrast echoes filling the right atrium (RA). **C,** contrast echoes have passed from the right atrium into the right ventricle (RV). **D,** contrast echoes have passed from the right ventricle into the left ventricle (LV) during ventricular systole (**black arrow**). The left atrium (LA) remains free of contrast echoes. IVS = interventricular septum; P = patch.

Muscular: Five patients with patched muscular defects had obvious detachment of the patch which was present inferiorly in 4-chamber view (Fig. 6). This was confirmed by angiography and at reoperation in 3.

Diagnosis of intact VS by 2-D echocardiography: In 86 patients the VS appeared on 2-D echocardiography to be intact. In these patients, the patched VSD was inlet (7), subtricuspid (15), subaortic (47), muscular (9), subpulmonary (3), or doubly committed subarterial (5).

Fourteen had cardiac catheterization and angiography, and no residual shunt was found in 12. A minute jet of contrast medium was seen in the subtricuspid area in 1 patient and in the subaortic area in 1. No surgery was indicated in these 2 patients because the shunts were minute.

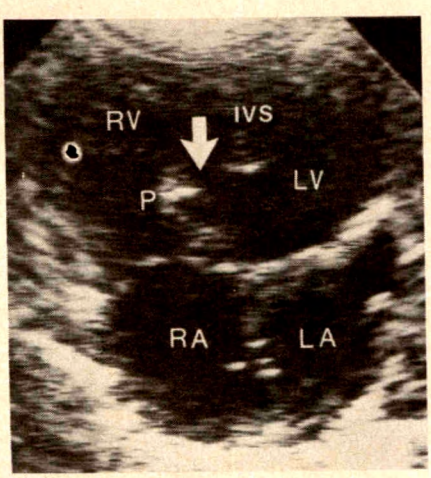

FIGURE 3. Two-dimensional echocardiographic apical 4-chamber view from a patient in whom inlet VSD has been patched but residual inferoposterior VSD persisted (**arrow**), confirmed angiographically and by surgery. IVS = interventricular septum; LA = left atrium; LV = left ventricle; P = patch; RA = right atrium; RV = right ventricle.

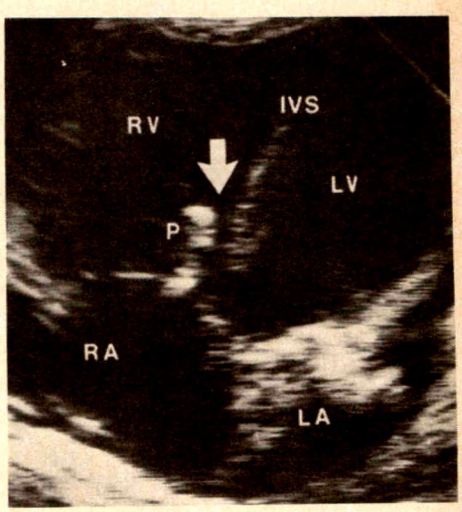

FIGURE 4. Two-dimensional echocardiographic apical 4-chamber view from a patient in whom a subtricuspid VSD has been patched, but a residual inferoposterior VSD persisted (**arrow**), confirmed angiographically. IVS = interventricular septum; LA = left atrium; LV = left ventricle; P = patch; RA = right atrium; RV = right ventricle.

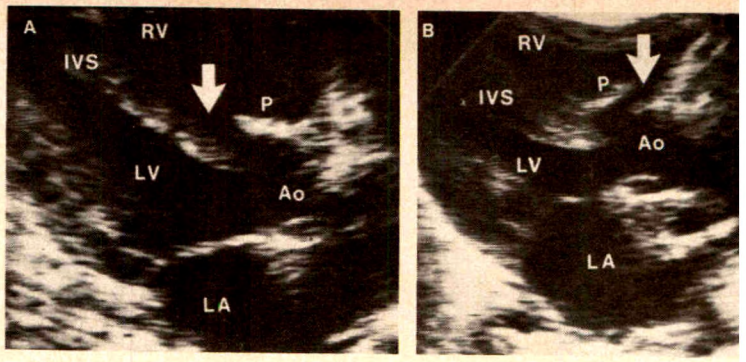

FIGURE 5. Two-dimensional echocardiographic parasternal long-axis view in 2 patients in whom subaortic VSDs had been patched but residual anteroinferior (**A**) and anterosuperior (**B**) VSDs persisted (**arrows**), both confirmed angiographically and by surgery. Ao = aortic valve; IVS = interventricular septum; LA = left atrium; LV = left ventricle; P = patch; RV = right ventricle.

Sixty-nine of the 72 patients with neither echocardiographic signs of residual VSD nor invasive investigation had no clinical sign of persistent VSD. Three had a pansystolic murmur suggesting a residual shunt, but no drop-out was seen around the patch, nor could another defect be seen.

Discussion

Two-dimensional echocardiography has been shown to be a good method for displaying dense structures such as a Dacron® patch inside the heart. The position of the patch on the VS delineates the anatomic type of defect because the patch shows brighter echoes than the VS and the interface between them is easily visualized.

In 15 patients with angiographic proof of residual shunt the 2-D echocardiogram was correct in 13 (86%). In the 2 patients in whom the VSD was not detected by 2-D echocardiography, the measured shunts were <1.5:1 and so the defect, although present, was hemodynamically insignificant. Among the 17 patients with clinical signs of residual shunt who did not undergo invasive investigation, 2-D echocardiography showed signs of detachment in 14 (82%), suggesting that 2-D echocardiography was correct. In the 3 patients in whom 2-D echocardiography had not shown a residual VSD although clinical signs suggested its presence, the leaks may have been too minute to be detected.

Small leaks underneath the patch due to loose stitches or detachments which are smaller than the resolution power of the ultrasound beam could not present any detectable echocardiographic drop-out.

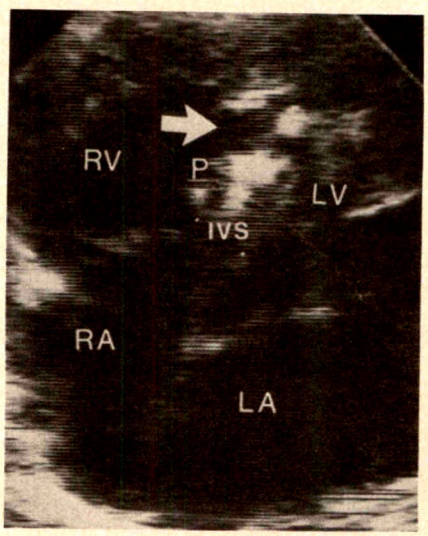

FIGURE 6. Two-dimensional echocardiographic apical 4-chamber from a patient in whom a central muscular VSD had been patche residual posteroinferior VSD persisted (**arrow**), confirmed a graphically. IVS = interventricular septum; LA = left atrium; LV ventricle; P = patch; RA = right atrium RV = right ventricle.

In the 73 patients with no clinical sign of resi shunt who did not have postoperative invasive in tigation, 2-D echocardiography showed no VSD in thus, the echocardiographic diagnosis of intact was correct in 94%. In 4 false-positive cases, 2 prese an important malalignment of the septum and

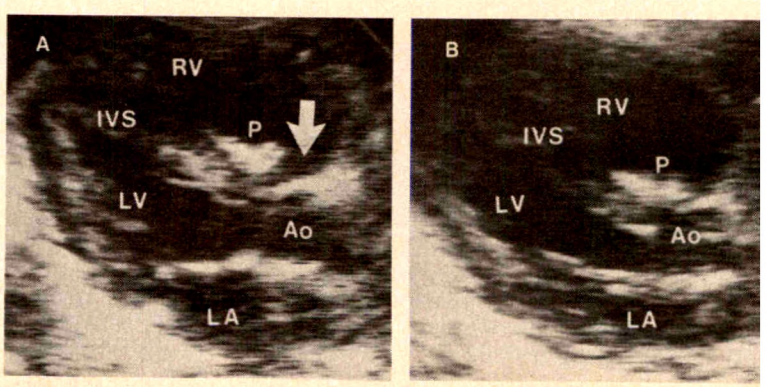

FIGURE 7. Two-dimensional echocardiographic parasternal long-axis view from a patient with patched subaortic VSD and no clinical signs of residual shunt. **A,** immediate postoperative assessment showing a drop-out between the patch (P) and the anterior wall of the aorta (Ao). **B,** 2 months later, the drop-out had disappeared. IVS = interventricular septum; LA = left atrium; LV = left ventricle; RV = right ventricle.

echocardiography was done in the immediate postoperative period.

Of 15 patients in whom angiography showed an intact VS, 2-D echocardiography predicted that this was correct in 12 (80%). In 1 patient the patch was in an angled position, giving the appearance of discontinuity between septum and patch. In 2 patients studied in the first postoperative fortnight, there was a persistent drop-out between VS and patch. The patients were restudied 1 to 2 months later and the echocardiographic drop-out had disappeared (Fig. 7). This false-positive echocardiographic appearance was probably peripatch edema of the VS or hematoma. It is possible that pulsed Doppler echocardiography[8] will provide additional information for detecting small shunts in patients who have physical signs of residual VSD but nothing obvious on 2-D echocardiography, and for ruling out shunts in those who have no clinical signs of residual VSD but echocardiographic drop-outs suggesting VSD. Although minute VSDs were missed, real-time echocardiography has been a reliable noninvasive technique for detecting significant residual shunt and intact VS after surgical closure of VSD.

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Postmortem Digoxin Tissue Concentration and Organ Content in Infancy and Childhood

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The concentration of digoxin in tissues and the content of the drug in various organs are reported in 36 infants and children. Sixteen received the drug on a short-term basis and 20 on a long-term basis. The drug was given intravenously to 12, orally to 17, and by intramuscular injection to 7. The study was conducted to determine distribution of digoxin in infants and children and to examine the forensic implications related to digoxin overdosage. Upper therapeutic concentration thresholds for digoxin were established in various tissues. These are different for preterm and full-term neonates than for older children and adults; for example, adult and neonatal values for postmortem blood specimens are 8 and 15 ng/ml, and for ventricular myocardium are 250 and 450 ng/g, respectively. The chronically digitalized premature infant retains in most tissues a considerably larger fraction of digoxin than more mature infants and children. This is in accord with previously demonstrated lower renal digoxin levels in premature infants attributed to their reduced ability to excrete this drug.

Tissue concentrations of digoxin have been reported in few infants and children.[1–6] Variables that affect the tissue concentration of digoxin include age, dosage, duration of treatment, and route of administration. We present the tissue concentrations of digoxin at autopsy in 36 infants and children, 16 of whom received the drug on a short-term and 20 on a long-term basis. The data are important in understanding the distribution of digoxin in different age groups, and for forensic purposes.

Methods

Thirty-six patients aged 1 day to 18 years who received digoxin and died from congenital heart disease were studied. None had clinical or electrocardiographic signs of toxicity. Blood and tissue samples from various organs were obtained at autopsy according to a specific protocol. Serum digoxin concentrations were measured within several days before death and within 24 hours after death. The digoxin concentration in each organ was measured by previously reported methods[2,3] and was expressed as nanograms/gram of wet tissue or nanograms/milliliter of blood or bile. The patients were subdivided into a short-term (acute) group (AcG) who received the drug for ≤3 days (n = 16) and a long-term (chronic) therapy group (ChrG), who received it for >3 days (n = 20). They were further subdivided into groups representing age and maturity, such as premature neonates (n = 12), full-term neonates (n = 12), children <2 (n = 5), and children >2 years (n = 7), and into groups receiving intravenous (n = 12), oral (n = 17), or intramuscular (n = 7) digoxin.

Pertinent clinical data and digoxin dosage are shown in Table I. Postmortem content of digoxin in various organs was calculated by multiplying the tissue concentration of the drug by the organ weight. The weights of the heart, kidneys, liver, spleen, lungs, brain, adrenal glands, and pancreas were measured directly at autopsy. The weights of blood volume, skeletal muscle, skin, fat, stomach, small and large intestines, gall bladder, bile, urinary bladder, thymus, thyroid, and gonads were derived from standard reference tables applicable to our age and weight groups.[7] Samples from brain, kidney, and adrenal glands were obtained from the cortical area. Statistical analysis included paired and unpaired t tests to determine differences between groups.

Results

Digoxin tissue concentrations are shown in Table II and the organ content of digoxin in Table III.

Digoxin tissue concentrations: The digoxin concentration of postmortem blood samples was always higher than that in premortem samples. In premature and full-term neonates, pre- and postmortem blood digoxin concentration tended to be higher than that of older children in both the AcG and ChrG. The highest values were 4.0 ng/ml in premortem and 14.1 ng/ml in postmortem blood samples, both from premature infants. Four preterm infants had premortem blood levels

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TABLE I Clinical Data

		Age	Weight (kg)	BSA (m^2)	Route of Admin	Duration of Admin	Digoxin Dosage: Loading (μg)	Digoxin Dosage: Dose (μg/kg)	Maintenance Dose (μg/day)	Maintenance Dose (μg/kg/day)
Acute										
Premature infants	mean	2 days	1.8	0.15	IM 2	1.0 days	32	20	...	...
	SD	1	0.6	0.03	IV 1	0	9	11	...	...
	n	4	4	4	PO 1	4	4	4	...	...
Full-term infants	mean	7 days	3.2	0.22	IM 2	1.9 days	132	42	...	...
	SD	5	0.4	0.02	IV 5	0.9	65	17	...	...
	n	9	9	9	PO 2	9	9	9	...	...
Children >2 years	mean	10 yr	24.0	0.91	IV 3	1.3 days	353	17	...	...
	SD	1	3.9	0.15	...	0.58	231	14	...	...
	n	3	3	3	...	3	3	3	...	...
Chronic										
Premature infants	mean	13 days	1.4	0.12	IM 3	6.8 days	...	...	8	5
	SD	5	0.4	0.03	IV 2	2.0	...	...	5	2
	n	8	8	8	PO 3	8	...	...	8	8
Full-term infants	mean	12 days	3.6	0.23	IV 1	5.7 days	...	...	65	17
	SD	4	0.8	0.04	PO 2	1.5	...	...	34	7
	n	3	3	3	...	3	...	...	3	3
Children <2 years	mean	12 mo	5.9	0.31	PO 5	2.9 mo	...	...	104	18
	SD	10	2.5	0.10	...	3.4	...	...	40	2
	n	5	5	5	...	5	...	...	5	5
Children >2 years	mean	12 yr	23.8	0.94	PO 4	3.7 yr	...	...	225	10
	SD	7	13.4	0.35	...	6.9	...	...	50	5
	n	4	4	4	...	4	...	...	4	4

Admin = administration; BSA = body surface area; IM = intramuscular; IV = intravenous; PO = oral; SD = standard deviation.

≥3 ng/ml (3.0, 3.5, 3.9, and 4.0), and 3 had a postmortem digoxin concentration >10 ng/ml (12.0, 14.1, and 11.5). Three full-term neonates had premortem blood levels ≥3.0 ng/ml (3.0, 3.2, and 3.7) and only 1 had a postmortem blood digoxin concentration of >10 ng/ml (12.7).

In right (RV) and left (LV) ventricular myocardium, the digoxin concentration was not significantly different in the AcG. In the ChrG, the RV concentration tended to be lower than the LV, but this was not evident in all subsets. In both short- and long-term groups, myocardial digoxin concentration was lower in older children compared with preterm and full-term neonates. No statistically significant difference occurred between the myocardial concentrations in the latter 2 groups. In 1 premature infant, both LV and RV myocardium had a digoxin concentration of >400 ng/g (456 and 431 ng/g, respectively). This also occurred in the left ventricle of 1 full-term neonate (450 ng/g). Average values for LV and RV digoxin concentration were more than 150 ng/g in all neonates. In children <2 years of age, the mean RV and LV digoxin concentration values were >125 and 150 ng/g, respectively. In older children, myocardial digoxin levels in the AcG were about 100 ng/g and those in the ChrG were lower. Digoxin levels in atrial myocardium were generally lower than those in ventricular myocardium.

Renal digoxin concentration showed great variability and no significant age differences in the ChrG. Mean values were 131 to 291 ng/g. Older children had similar renal digoxin values in the AcG and ChrG; however, in premature infants in the AcG these values were significantly lower (mean 71 ng/g).

Skeletal muscle and skin digoxin concentration showed no significant differences between AcG and ChrG and among the various age groups; mean values were 17 to 48 ng/g in the former and 9 to 35 ng/g in the latter. Adipose and splenic tissue digoxin levels were low (11 and 18 ng/g, respectively) in all age groups and subsets.

The digoxin concentration in lung tissue ranged from 26 to 37 ng/g except in the older children in the ChrG, in whom it was 12 ng/g. Adrenal cortical digoxin levels tended to be lower in older children in the ChrG but not in the AcG. In urinary bladder, thymus, thyroid, and gonad (of either sex) samples, the digoxin concentration did not show appreciable difference with age in the AcG; in the ChrG, it tended to be lower in older children. The digoxin concentration in cerebral cortex specimens was low, usually <20 ng/g. It was lower in AcG than in ChrG and there was no significant difference between age groups. In the liver and hollow gastrointestinal viscera (stomach, small and large intestine, and gall bladder), the digoxin levels were variable. They were lower in older children. The highest values were found in small intestine and gall bladder.

Digoxin content of organs: The postmortem digoxin content of the organs was expressed as a percentage of the dosage administered. For the AcG, the total loading dose of digoxin was used as a reference; for the ChrG, the daily maintenance dose was used.

Acute group: In preterm infants, an average of 59% of the total dose of digoxin administered was recovered from the body tissues analyzed; in full-term neonates, 52% was recovered and in older children, 73% of digoxin was recovered. The differences between age groups were not statistically significant.

Most digoxin was recovered from skeletal muscle, that is, one fifth to one third of the dose administered; significant amounts were also extracted from heart (4 to 7%), kidneys (2 to 4%), skin (3 to 6%), fat (2 to 7%), lung (2 to 3%), brain (2%), and blood (0.4 to 1%) samples. In the gastrointestinal tract, values were liver 5 to 7%, pancreas 0.2 to 1%, stomach 0.2 to 0.4%, small intestine

TABLE II Digoxin Concentration in Tissues

		Blood										
		Antemortem	Postmortem	LV	RV	RA	LA	Kidneys	Skeletal Muscle	Skin	Fat	Liver
Acute												
Premature	mean	2.9	8.6	165	179	...	...	71	19	9	6	37
infants	SD	0.8	3.1	138	91	...	...	66	25	9	7	46
	n	4	3	3	3	...	...	3	4	4	4	4
Full-term	mean	2.4	8.7	237	228	156	138	231	38	34	9	74
infants	SD	0.7	3.2	68	159	59	70	153	29	38	4	53
	n	8	4	9	9	8	8	8	8	8	8	8
Children	mean	1.0	3.1	107	101	71	56	122	17	15	5	37
>2 years	SD	0.3	0.2	40	67	12	33	98	8	7	3	10
	n	3	2	3	3	3	2	3	3	3	3	3
Chronic												
Premature	mean	2.3	9.1	235	226	159	160	155	28	18	11	86
infants	SD	1.0	4.7	97	95	85	37	128	13	12	6	39
	n	8	4	8	8	4	4	8	8	7	5	8
Full-term	mean	2.6	5.2	296	207	210	166	171	46	35	8	103
infants	SD	0.7	1.3	135	34	31	4	69	14	23	4	55
	n	3	2	3	2	3	2	3	3	3	3	3
Children	mean	1.2	3.2	127	130	68	88	291	48	30	11	75
<2 years	SD	0.3	0.2	94	76	65	70	397	55	26	12	76
	n	5	2	4	3	4	3	4	4	4	5	4
Children	mean	0.9	3.5	86	56	32	23	131	31	18	3	39
>2 years	SD	0.3	1.1	54	31	23	16	118	37	24	4	28
	n	4	2	4	4	3	3	4	4	3	4	4

LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; SD = standard deviation. Values are expressed as nanograms/gram

3 to 6%, large intestine 0.3 to 1%, and gall bladder 0.3 to 0.2%. The spleen, adrenals, urinary bladder, thymus, thyroid, and gonad each contained <1% of the total dose administered.

Chronic group: The total amounts of digoxin recovered from the various organs analyzed, expressed as a percentage of the daily maintenance dose, were 458% in preterm infants, 144% in full-term neonates, 118% in children under 2 years, and 199% in older children. Premature infants retained a significantly greater fraction of the daily maintenance dose. In the ChrG, large quantities of digoxin were found in skeletal muscle (145% in premature infants and 38 to 124% in the older age groups), heart (83% in premature infants and 4 to 15% in older children), kidneys (25% in premature infants and 8 to 13% in older children), skin (32% in premature infants and 8 to 9% in older infants), fat (24% in premature infants and 6 to 9% in older children), brain (17% in premature infants and 9 to 15% in older children), and blood (3% in premature infants and 0.5 to 1% in older children) specimens.

The organs of the gastrointestinal tract also contained significant amounts of digoxin: liver (57% in premature infants and 13 to 20% in older children), pancreas (1% in premature infants and 0.2 to 1.4% in older children); stomach (3% in premature infants and 1% in older

TABLE III Organ Content of Digoxin Expressed as Percentage of Dose

		Blood	Ventricles	Atria	Total Heart	Kidneys	Skeletal Muscle	Skin	Fat	Liver	Spleen
Acute											
Premature	mean	1	6	1	7	2	26	4	3	5	0.2
infants	SD	0.3	3	1	4	1	20	3	2	5	0.03
	n	4	3	3	3	3	4	4	4	4	3
Full-term	mean	0.4	4	1	5	4	20	3	2	6	0.4
infants	SD	0.1	3	0.4	4	2	16	4	1	4	1
	n	8	8	8	7	8	8	8	8	8	8
Children	mean	0.5	4	0.4	4	3	35	6	7	7	0.3
>2 years	SD	0.1	2	0.2	2	2	12	3	3	1	0.1
	n	3	3	3	3	3	3	3	3	3	3
Chronic											
Premature	mean	3	64	9	83	25	145	32	24	51	2
infants	SD	1	28	3	16	24	77	17	16	35	2
	n	8	8	4	4	8	8	7	5	8	6
Full-term	mean	1	9	1	10	10	56	8	6	20	0.4
infants	SD	0.3	2	0.3	3	4	23	6	3	12	0.2
	n	3	3	3	3	3	3	3	3	3	3
Children	mean	0.5	4	0.4	4	13	38	9	7	16	0.3
<2 years	SD	0.2	2	0.2	2	11	34	4	5	8	0.2
	n	5	4	4	4	4	4	4	5	4	3
Children	mean	1	13	1	15	8	124	9	9	13	0.4
>2 years	SD	0.3	13	1	9	7	121	11	10	8	0.2
	n	4	4	4	4	4	4	3	4	4	4

SD = standard deviation.

TABLE II (continued)

Spleen	Lung	Brain	Adrenal Glands	Pancreas	Stomach	Small Intestine	Large Intestine	Gall Bladder	Bile	Urinary Bladder	Thymus	Thyroid	Gonad
11	26	3	17	32	20	40	24	25	...	15	12	28	13
3	7	1	15	11	7	31	39	5	...	7	5	4	6
3	3	2	3	3	4	4	4	3	...	2	3	3	2
18	37	8	40	34	31	269	80	85	...	20	20	37	22
10	19	6	19	14	17	478	50	42	...	8	...	20	15
8	8	6	6	6	8	8	8	7	...	5	...	7	7
15	28	6	50	160	18	48	22	287	...	16	145	19	18
6	16	5	34	232	10	5	15	47	...	...	...	10	2
3	3	3	2	3	3	3	3	2	...	1	1	3	2
15	32	7	32	34	35	135	121	101	89	25	25	33	16
6	9	3	4	20	20	209	93	104	86	19	4	16	12
6	6	6	5	7	8	8	7	5	4	3	4	4	3
18	30	20	26	68	43	114	60	85	...	36	20	51	38
10	20	21	13	47	24	74	64	57	...	...	15	7	34
3	2	2	3	3	3	3	3	3	...	1	2	2	2
18	33	32	29	41	39	92	85	175	205	22	26	9	24
22	49	25	36	62	54	142	116	121	...	24	38	2	30
3	3	3	4	4	4	4	4	3	1	3	4	3	3
7	12	14	12	13	54	66	32	18	...	5	...	19	3
5	8	16	10	15	68	75	34	20	...	...	...	16	...
4	4	2	3	2	4	3	4	4	...	1	...	3	1

wet tissue except for blood and bile, which are expressed as nanogram/milliliter.

children); small intestine (42% in premature infants and 4 to 6% in older children); large intestine (1% in premature infants and 1 to 6% in older children); gall bladder (0.3% in premature infants and 0.03 to 0.1% in older children); and bile (1% in both premature infants and older children). Other organs (adrenal glands, urinary bladder, thymus, thyroid, and gonads) each contained ≤1% of the maintenance dose of digoxin administered.

Effect of dosage, route, and duration of administration: It was not possible to determine significant differences of tissue distribution with respect to the route of administration and dosages given. Premature and full-term neonates in the AcG tended to have lower values than those in the ChrG; this was not observed in older children.

Discussion

The present data improve the understanding of the body distribution of digoxin in infants and children and the forensic medical aspects of fatal overdosage of the drug. Previous information regarding digoxin tissue concentrations and organ contents in the pediatric age group has been fragmentary.[1–6]

Significant differences exist between serum digoxin concentration obtained pre- and postmortem,[8] and the

TABLE III (continued)

Lung	Brain	Adrenal Glands	Pancreas	Stomach	Small Intestine	Large Intestine	Gall-Bladder	Bile	Urinary Bladder	Thymus	Thyroid	Gonads
3	2	0.2	0.3	0.4	3	1	0.03	...	0.06	0.2	0.1	0.3
1	1	0.2	0.09	0.01	2	1	0.005	...	0.003	0.2	0.03	0
3	2	3	3	4	4	4	3	...	2	3	3	2
3	2	0.2	0.2	0.2	6	1	0.04	...	0.04	0.02	0.04	0.02
2	2	0.1	0.1	0.1	12	1	0.01	...	0.01	0.09	0.02	0.02
8	6	6	6	8	8	8	7	...	5	6	7	7
3	2	0.1	1	0.3	3	0.3	0.2	...	0.09	0.1	0.03	0.01
1	2	0.05	2	0.1	0.4	0.4	...	...	...	...	0.01	...
3	3	2	3	3	3	3	2	...	1	1	3	2
11	17	1	1	3	42	15	0.3	1	1	1	0.04	0.1
4	11	0.4	1	2	71	12	0.3	1	0.1	1	0.04	0.1
8	6	5	7	8	8	8	5	4	3	4	4	3
3	15	0.2	0.4	1	6	6	0.08	...	0.2	0.3	0.1	0.09
2	9	0.2	0.4	1	4	4	0.05	...	...	0.3	0.02	0.08
2	2	3	3	3	3	3	3	...	1	2	2	2
3	18	0.1	0.2	1	4	2	0.1	1	0.04	0.5	0.02	0.03
3	11	0.1	0.1	0.4	6	2	0.1	...	0.03	0.5	...	0.03
3	3	4	4	4	4	4	3	1	3	4	3	3
2	9	0.04	0.2	1	6	1	0.03	...	0.1	...	0.07	0.01
2	10	0.04	0.2	1	5	1	0.05	...	...	...	0.07	...
4	2	3	2	4	11	4	4	...	1	...	3	1

latter may show significant site variability. In adults, the mean post- to premortem digoxin concentration ratio was 1.96 to 2.33 for heart, 1.63 for subclavian, 1.38 to 1.42 for femoral, and 1.84 for jugular venous blood specimens.[8,9] No significant differences were found between pre- and postmortem blood samples obtained ≤30 minutes after death.[10] For longer periods, no correlation was observed between postmortem period and blood digoxin concentration; this suggested that a new equilibrium is established after death.[8,10]

The mean digoxin concentration ratio between whole blood and serum was 1.3[11]; this reflects the binding of most glycoside to the erythrocyte membrane. The erythrocyte: plasma digoxin ratio is less in the AcG than in the ChrG, 1.00 ± 0.43 and 3.62 ± 2.00 (± standard deviation), respectively.[6]

In 1969, Hernandez et al[1] studied the pharmacodynamic features of digoxin in infants using tritiated digoxin. These radioisotope data, although extremely useful with regard to kinetics, cannot be readily converted into tissue concentrations. Our own laboratory reported tissue concentrations of digoxin obtained at surgery in 1974[2] and autopsy in 1975[3] in infants and children. Neonates had higher concentrations in the RV and LV myocardium than older children and adults. Renal concentrations were lower in preterm than full-term neonates and older children. Andersson et al[4] published data on tissue levels in 12 infants and 17 adults. The digoxin concentration was significantly higher in myocardium and kidney samples from infants.

Lang et al[5] in 1978 reported tissue and plasma digoxin levels in 13 premature and 6 full-term newborns, and 5 older infants. Tissue digoxin levels tended to be higher in premature and full-term newborns than in mature infants. This difference was statistically significant in myocardium and skeletal muscle. The renal digoxin concentration was lower in premature than in mature neonates; the tissue concentrations of other organs were essentially equal in these groups. No significant difference in the ratio of myocardium and plasma digoxin was found among the various age groups.

Gorodischer et al[6] in 1976 examined the distribution of digoxin in myocardium skeletal muscle, and plasma in 8 infants and children and the digoxin concentration in erythrocytes and plasma in 16 patients. Some of the values for myocardium, skeletal muscle, and serum concentrations were considerably higher than those observed by other investigators. The mean myocardial digoxin concentration was 386 ng/g; it was ≥483 ng/g in 4 of the 8 children studied. The highest myocardial concentration was 975 ng/g. These data can probably be explained by the short dose-autopsy interval (0.75 to 6 hours) and the large digitalizing doses given.[6]

In the present study, neonates who received therapeutic doses of the drug had higher levels in several tissues than older children. These differences were especially striking for myocardium, liver, and the gastrointestinal tract. Digoxin concentrations in the AcG tended to be lower than those in the ChrG in premature and full-term infants, but not in older children. The digoxin concentration in premortem blood samples was <4 ng/ml in infants and <2 ng/ml in older children. Postmortem blood samples obtained from the heart had maximal levels of <15 ng/ml in neonates and <5 in older children. Ventricular myocardial digoxin levels were generally >200 ng/g in neonates, but measured 160 to 180 ng/g in AcG preterm infants. Older children had levels of ≤100 ng/g. Acutely digitalized premature infants had lower renal digoxin levels, because of their reduced ability to excrete the drug. No significant differences in renal digoxin levels were noted among the other age groups. Because of the variability of its digoxin concentration, the kidney does not represent a good organ from which to judge toxicity.

Skeletal muscle is the major repository for digoxin and, as shown in this study, its digoxin concentration has a narrow range. Liver tissue is another useful marker of digoxin toxicity. Lung digoxin levels are low in chronically digitalized children, but are higher in full-term neonates, especially premature infants. This may be related to the greater compactness of premature lung tissue. The concentration of digoxin in the gastrointestinal tract varies markedly and is often high even when the drug is administered parenterally. In adults, as much as 30% of a digoxin dose may be excreted in the bile within 24 hours, resulting in a significant enterohepatic cycle.[12,13] Digoxin excretion into the bowel, through the bowel wall itself, has also been proposed.[13]

Digoxin is concentrated in specific areas of the brain, for example, the choroid plexus of the fourth ventricle.[14] In cases of toxicity, digoxin may also be concentrated in other areas, such as the area postrema (chemoreceptor trigger zone) nucleus of the vagus and optic apparatus.[15,16] This distribution may explain symptoms of digoxin toxicity.

With chronic digoxin administration, the amount of drug retained in the tissues was strikingly higher in preterm infants—from 4 to 5 times the daily maintenance dose—than in older children, who retained 1 to 2 times this dose.

Doherty et al[17] reported the half-time of digoxin distribution in tissue samples to be 30 minutes after intravenous administration and 50 minutes after oral ingestion in liquid form. As a consequence, one would expect, after an intravenous dose, that 50% of the maximal concentration would occur in the tissues by 0.5, 75% by 1, and 94% by 2 hours.

Reissel et al[18] considered levels of ≥8 ng/ml in postmortem blood samples and ≥250 ng/g in ventricular myocardium specimens to represent toxic levels in adults. On the basis of the present data, the corresponding toxic postmortem concentrations in neonates are much higher, that is, 15 ng/ml in postmortem blood samples, and 450 ng/g in ventricular myocardium specimens. In the absence of blood or myocardium, liver and skeletal muscle are the alternative tissues of choice for toxicologic analysis of digoxin. Kidney tissue is not a reliable indicator of toxicity. Spiehler et al[14] suggested that the digoxin content of medulla, under the obex, may be useful in confirmation of the elevated blood digoxin concentration.

The present study enlarges on reports of tissue distribution of digoxin: the limits of toxicity in infants and children can be determined with greater confidence based on this larger and more comprehensive series.

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Masked Subaortic Stenosis in Ostium Primum Atrial Septal Defect: Recognition and Treatment

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Five patients with ostium primum atrial septal defect (ASD) and a cleft mitral valve had no hemodynamic evidence of left ventricular (LV) outflow tract obstruction on preoperative cardiac catheterization. After surgical closure of the ASD and repair of the mitral cleft, all 5 patients manifested subaortic stenosis with pressure gradients ranging from 10 to 120 mm Hg. Postoperative LV angiograms revealed systolic narrowing of the outflow tract, and the same outflow tract dynamics were recognized on reviewing the preoperative angiograms and echocardiograms. Persistence or exaggeration of the characteristic diastolic "goose-neck" deformity during LV systole in atrioventricular canal defects is diagnostic of a potential or actual subaortic obstruction. This diagnostic sign is also readily recognizable by 2-dimensional echocardiography, and when present, the surgeon should be alerted to explore the LV outflow tract because the outflow tract anatomy is not readily apparent at operation aimed solely at closing the ASD and repairing the cleft mitral valve.

Hemodynamic masking of left ventricular (LV) outflow tract obstruction by a large ventricular left-to-right shunt has been recognized as a diagnostic pitfall in congenital cardiac defects.[1,2] In contrast, the only known entity with intact ventricular septum in which stenosis of the LV outflow tract can be hemodynamically inapparent is ostium primum atrial septal defect (ASD) with a cleft mitral valve. Although mild LV outflow tract pressure gradients have been noted infrequently in ostium primum defects before intracardiac repair,[3,4] subaortic stenosis (SAS) is more readily recognizable during postoperative cardiac catheterization[5,6] or at autopsy.[7] In most such patients, anatomic narrowing of the LV outflow tract is already present preoperatively and can be recognized by angiography[3] and echocardiography.

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Methods

Between 1975 and 1981, 5 patients who presented with SAS after surgical repair of ostium primum ASD and cleft mitral valve were identified (Table I). In none of the 5 patients was SAS diagnosed before corrective surgery; however, a review of the preoperative angiograms (Fig. 1) in all 5 patients and the preoperative echocardiograms (Fig. 2) in 2 patients revealed anatomic features of the LV outflow tract that are characteristic of this variant of ostium primum defect.[3] Similarly, in none of the 5 patients was the LV outflow tract obstruction detected during initial surgical repair.

A prominent postoperative systolic murmur attributed clinically to residual mitral regurgitation prompted cardiac catheterization in all 5 patients an average of 4 years after primary surgical repair. Mitral regurgitation was mild in 2 patients, minimal in 1, and undetectable in 2 (Table I). However, unexpected pressure gradients across the LV outflow tract ranging from 10 to 120 mm Hg (mean 56) were found in all to explain the postoperative murmur. In 4 patients who had postoperative 2-dimensional echocardiograms, the LV outflow tract was tunnel-like, with systolic narrowing in 3 and, in addition, anomalous mitral valve attachments to the ventricular septum were noted in the fourth patient. Persistence of the goose-neck deformity during ventricular systole was observed in these patients both angiographically and echocardiographically. In 2 patients (DCA, DT) who had this typical systolic goose-neck deformity on preoperative angiograms, additional discrete stenosis of the LV outflow tract was evident postoperatively (Fig. 3), requiring reoperation.

FIGURE 1. Systolic goose-neck narrowing in preoperative left ventricular cineangiograms. **Top,** anteroposterior view (patient BD). **Bottom,** lateral view (patient DCH). **Arrows** indicate systolic increase in outflow tract narrowing. D = diastole; S = systole.

We surveyed preoperative LV angiograms in 22 additional unselected patients who had surgery to correct the ostium primum defect over the past 10 years. Three patients had no narrowing of the LV outflow tract throughout the cardiac cycle, 18 had the common diastolic goose-neck deformity, and only 1 patient had unequivocal dynamic systolic narrowing of the outflow tract. This same patient was catheterized after repair of the ostium primum defect and had no subaortic pressure gradient; angiographically, systolic narrowing of the LV outflow tract was no longer observed.

Surgical approach: Three patients had reoperation for hemodynamically significant SAS (Table I). Septal myotomy or myectomy, or both, was carried out in an attempt to enlarge the outflow tract in all 3 patients, and in 2, an additional fibromuscular ridge was resected. In the patient with the most severe SAS (DCH), cardiac catheterization and echocardiography after the first reoperation revealed marked residual SAS due to an excessively anterior attachment of the anterior mitral leaflet. At a second reoperation, the superior portion of the anterior mitral leaflet was detached from its original attachment to the crest of the ventricular septum and retracted posteriorly to create a large gap between the outflow septum and the valve leaflet. This gap was bridged with a pericardial patch which in effect relocated the mitral valve insertion posteriorly and thus enlarged the outflow tract. Because of an episode of endocarditis 2 months later, the mitral valve was replaced. An echocardiogram confirmed that the outflow tract has remained unobstructed 3 years after the last operation and the patient has remained symptom free.

Autopsy findings: A survey of anatomic specimens revealed 25 specimens of ostium primum ASD with associated anatomic narrowing of the LV outflow tract.[8] In 13 unoperated specimens, the narrowing was caused by an aneurysm of the membranous septum (1 specimen), excessive endocardial and

TABLE I Pertinent Catheterization and Operative Information in 5 Patients With Ostium Primum Atrial Septal Defect and Subaortic Stenosis

	Preoperative Catheterization						Operation (ASD + MCl)	Postoperative Catheterization						Reoperation			
			MR														
Patient	Age (yr)	Qp/Qs	LV → LA	LV → RA	LVSP (torr)	FASP (torr)	Age (yr)	Age (yr)	Shunt	Qp/Qs	MR LV → LA	LVSP (Torr)	AoSP (Torr)	Age (yr)	Shunt	MV	SAS
BD	1.2	1.9	++	±	95	95	2.8	4.5	ASD	1.7	+	...	...	...	...	...	...
								10.7	ASD	2.1	±	115	105	10.9	+	Cleft	...
DCH	3.9	3.2	+	+	115	...	4.3	15.0	0	—	+	215	95	15.4	...	Cleft	Myotm
								17.9	0	—	±	200	104	18.7	...	Repos	Myect Patch
DCA	0.7	5.6	±	++	85	90	1.3	18.7	VSD	1.3	++	108	96	18.8	+	Rplac	...
								4.9	0	—	±	175	95	5.5	...	...	Myotm Myect Ridge
JE	0.2	3.0	++	+	85	70*	0.6†	1.6	0	—	0	100	90	...	...	...	...
DT	0.5	3.4	±	+	95	96‡	0.9	1.4	0	—	0	185	124	2.7	...	...	Myect Ridge

* Coarctation.
† Additional coarctation repair.
‡ Cuff pressure.
AoSP = aortic systolic pressure; ASD = atrial septal defect; FASP = femoral artery systolic pressure; LA = left atrium; LV = left ventricle; LVSP = left ventricular systolic pressure; MCl = mitral cleft; MR = mitral regurgitation; MV = mitral valve; Myect = myectomy; Myotm = myotomy; RA = right atrium; Repos = repositioning; Rplac = replacement; SAS = subaortic stenosis; VSD = ventricular septal defect.

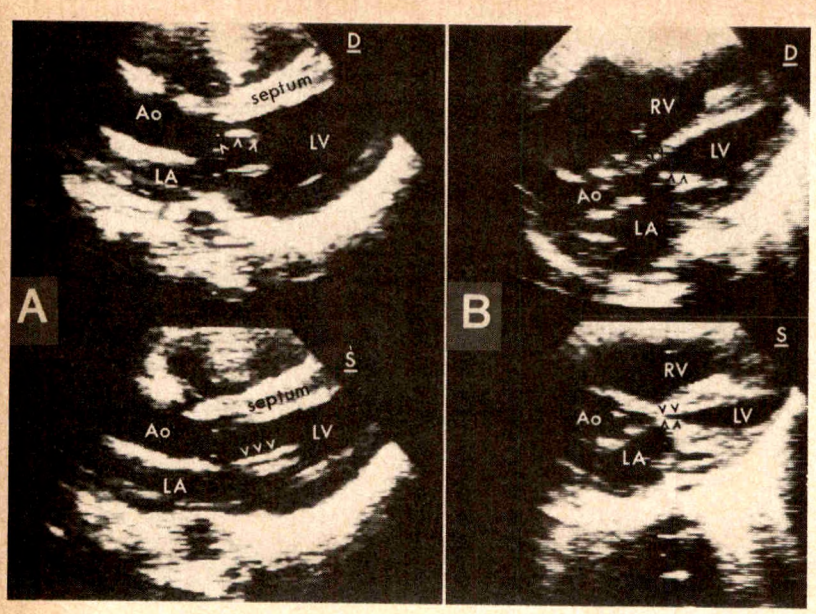

FIGURE 2. Preoperative 2-dimensional echocardiograms. **A,** uncomplicated ostium primum: left ventricular outflow tract narrow in diastole (**top**), wide in systole (**bottom**). **B,** patient DT with subaortic obstruction: outflow tract narrow in both diastole and systole. **Arrowheads** indicate position of the anterior mitral leaflet vis-à-vis the septum. Ao = aorta; D = diastole; LA = left atrium; LV = left ventricle; RV = right ventricle; S = systole.

chordal tissue (2 specimens), abnormal mitral valve attachments (4 specimens), generalized outflow tract hypoplasia (2 specimens) with additional anomalous mitral valve attachments (3 specimens), and an anomalous muscle bundle (1 specimen). In 12 postoperative specimens, the factors responsible for outflow narrowing were a discrete fibroelastic ridge (1 specimen), anomalous muscle bundle (2 specimens), abnormal mitral valve attachments (1 specimen), excessively reduced subaortic area after suture-closure of the large mitral cleft (7 specimens), and obstructive mitral prosthesis (1 specimen).

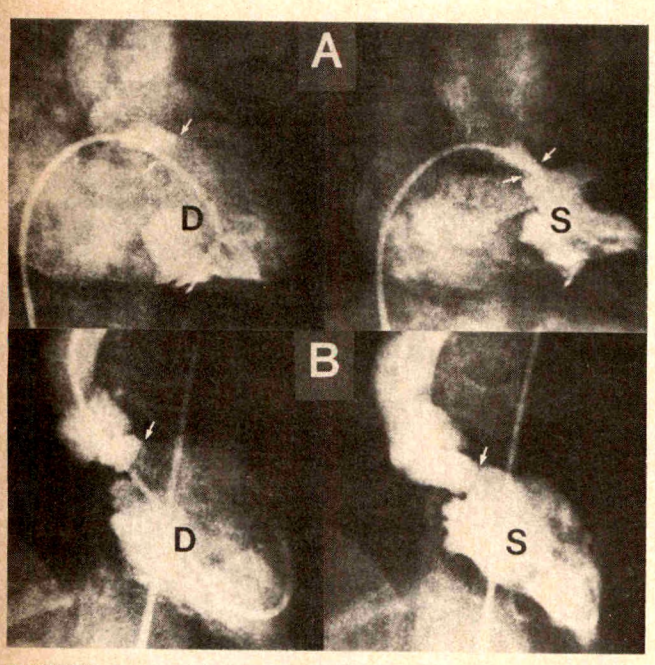

FIGURE 3. Left ventricular cineangiograms (anteroposterior view) in patient DCA. **A,** preoperatively, severe systolic outflow tract narrowing occurs simultaneously with massive mitral regurgitation; no subaortic pressure gradient is recorded. **B,** 5 years postoperatively, there is no mitral regurgitation and an 80 mm Hg pressure gradient is recorded across a discrete outflow ridge. **Arrows** indicate site of stenosis. D = diastole; S = systole.

Discussion

In this report, the term *ostium primum ASD* and the more anatomically appropriate terms *partial atrioventricular canal* and *partial atrioventricular septal defect*[9] are used interchangeably.

Because of the characteristic deficiency of the ventricular septum in atrioventricular canal defects and the abnormally anterior insertion of the mitral valve,[10] the outflow tract in ostium primum ASD becomes distorted, elongated, and narrowed (Fig. 4). The degree of this narrowing depends on the extent of septal deficiency, and in severe cases as much as three eighths of the septum may be absent.[11] In some patients the only remaining septum at the base is the conus septum.

The excavated smooth muscular septum and the abnormal mitral valve insertion produce the characteristic goose-neck appearance of the LV outflow tract during diastole in angiograms and echocardiograms. The extent of LV septal excavation and the potential for SAS can be assessed angiographically by the dynamics of the goose-neck deformity during the cardiac cycle (Fig. 5). Infrequently, an ostium primum defect with minimal septal excavation will have no goose-neck deformity in either diastole or systole (Fig. 5A). However, in most ostium primum defects, a moderate degree of septal excavation is reflected in a goose-neck deformity limited to diastole (Fig. 5B). In patients with more extensive outflow tract excavation and distortion who are at risk of developing SAS postoperatively, the diastolic goose-neck narrowing persists or becomes even narrower during systole (Fig. 5C). However, unless a critical point in this narrowing is reached, some patients in this category may not demonstrate resting LV outflow pressure gradients after repair of an ostium primum defect.

Preoperative hemodynamics in ostium primum defect apparently mask the severity of SAS even in patients in whom the LV outflow tract becomes critically narrowed during systole. After surgical repair of ostium

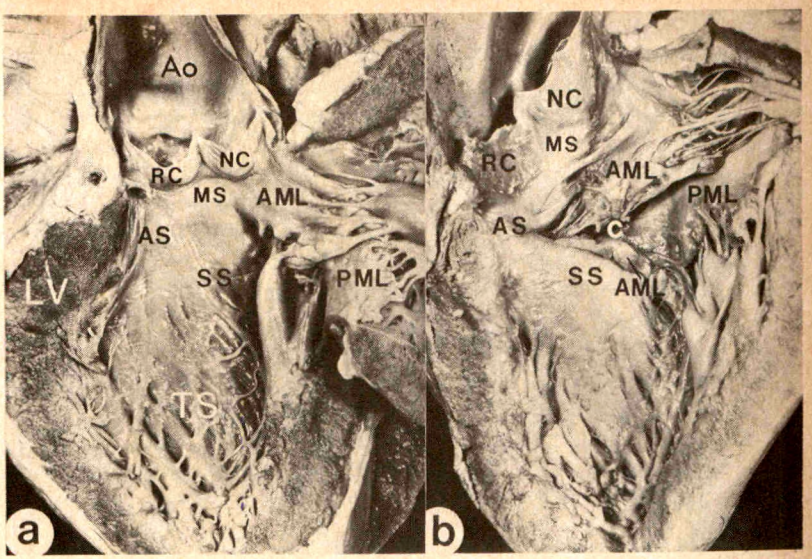

FIGURE 4. Left ventricular septal and outflow tract anatomy. **a,** normal heart demonstrating that the smooth sinus septum (SS) forms a major portion of the outflow area. **b,** in partial atrioventricular canal with severe deficiency of the smooth sinus septum, there is a large gap in the outflow tract which is filled by the anteriorly attached anterior mitral leaflet, producing subaortic narrowing. AML = anterior mitral leaflet; Ao = aorta; As = anterior septum; C = cleft; LV = left ventricular free wall; MS = membranous septum; NC = noncoronary cusp; PML = posterior mitral leaflet; RC = right coronary cusp; TS = trabeculated septum.

primum defect with a cleft mitral valve, the following mechanisms may contribute to the development of LV outflow tract pressure gradients: (1) The creation of a less mobile single valve leaflet from freely mobile cleft components may significantly limit the systolic travel of the anterior mitral leaflet from its diastolic position in the narrow outflow tract. (2) In the preoperative state, anomalous chordal or papillary muscle attachments of the cleft leaflets to the septum may not restrict leaflet mobility significantly; however, after cleft repair, the surgically fashioned single leaflet is more likely to remain anchored in the outflow tract by these attachments throughout the cardiac cycle. (3) Closure of the cleft and of the ASD eliminates the systolic LV vent to the right atrium and may produce an outflow pressure gradient by similar changes in hemodynamics, as observed in occult SAS after closure of a large ventricular septal defect.[1] (4) Significant mitral regurgitation reduces the effectiveness of the left ventricle as a forward pump; after cleft repair, the improved forward output and the increased systolic velocity of blood flow in the narrowed outflow tract may unmask a potential stenosis. (5) An obstructive fibrous ridge may develop postoperatively on the septal surface of a significantly narrow outflow tract as a result of increased turbulent flow and can in time produce pressure gradients.[3] (6) Any additional abnormality in the outflow tract (e.g., excessive septal bulge,[12] primary discrete SAS, aneurysm of the membranous septum,[13] anomalous muscle bundles, or papillary muscles or chordae) may become more obstructive after surgical repair of ostium primum defect due to mechanisms 1 to 4 just listed.

Why, then, are LV outflow tract gradients not noted more frequently at postoperative cardiac catheterization after ostium primum ASD repair? First, mild outflow tract stenoses responsible for postoperative apical ejection murmurs may clinically be attributed to residual mitral regurgitation,[14] and cardiac catheterization may not be recommended. Second, hypoplasia of the outflow tract is generally less severe in partial than in complete atrioventricular septal defect;[11] thus, critical hemodynamic narrowing is uncommon. Third, increasing the cardiac output by exercise or isoproterenol might produce pressure gradients in patients with less critical LV outflow narrowing who have no resting pressure gradient.

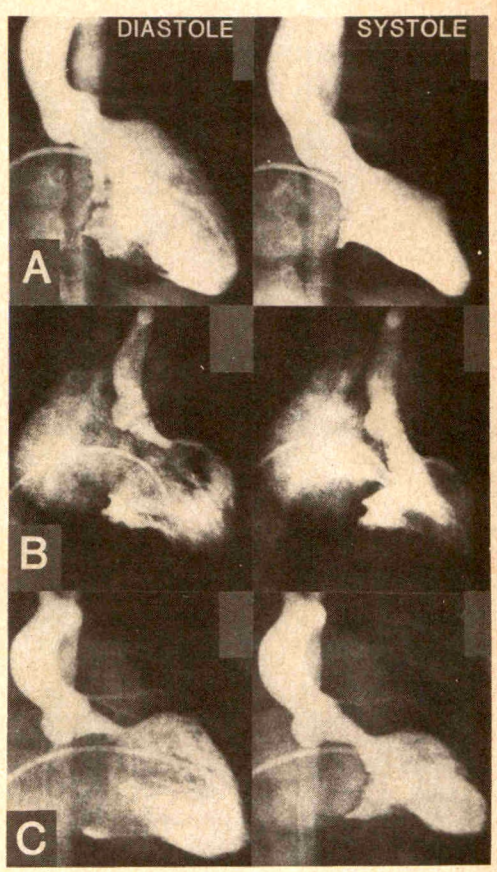

FIGURE 5. Angiographic variants of left ventricular outflow tract anatomy in ostium primum defect. **A,** rare "benign" form with no goose-neck deformity in either diastole or systole. **B,** common form with goose-neck deformity in diastole only. **C,** rare potentially obstructed form with goose-neck narrowing in both diastole and systole.

The foregoing observations indicate that surgical methods to eliminate or reduce LV outflow tract narrowing in these patients cannot be uniform. Nevertheless, hypoplasia of the subaortic area is common to most atrioventricular canal defects and removal of the discrete components alone may not always solve the problem completely or permanently. In our 3 reoperated patients, removal of a cube of septal myocardium to enlarge the outflow tunnel was performed in addition to resection of a discrete ridge stenosis, when present. However, when hypoplasia is too severe, the outflow tract may have to be enlarged more extensively to eliminate the obstruction. This can be accomplished by disconnecting the superior portion of the anterior mitral leaflet from its fusion with the ventricular septum, retracting it toward the left atrium and bridging the created gap with pericardium or other suitable synthetic material.

Because the anatomy of the LV outflow tract in ostium primum defect is not readily apparent during surgical approach aimed simply at closing the ASD and repairing the cleft of the mitral valve, patients at risk of manifesting SAS postoperatively must be identified before surgery by angiography and echocardiography. Even in the absence of surgically significant outflow pressure gradients, the presence of the characteristic systolic goose-neck narrowing preoperatively should alert the cardiologist to recommend surgical exploration of the LV outflow tract as part of the primary operative procedure or, at the least, insist on pressure measurements in the aorta and the left ventricle at the conclusion of ostium primum defect repair.

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Mechanisms of Closure of Perimembranous Ventricular Septal Defect

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Although more defects in the muscular ventricular septum close spontaneously than do defects abutting on the membranous septum (perimembranous defects), a good proportion of the latter show a tendency to diminish in size and to close. The mechanism responsible for this closure is usually described as an aneurysm of the membranous septum, although some doubt has been cast as to whether this is the precise mechanism. In this study, 69 unoperated hearts with ventricular septal defect were examined; 26 (38%) showed some evidence of partial closure and none extended exclusively into the outlet part of the septum. Two thirds of the trabecular perimembranous defects, almost half of the inlet defects, and one third of the confluent defects showed signs of partial occlusion. The anatomic structures most frequently responsible were reduplication of tricuspid valve tissue (16 cases), adhesion of tricuspid valve leaflets (6 cases), and prolapse of an aortic valve leaflet (3 cases). Only in 2 cases were subaortic tissue tags observed which might have originated from the remnant of the membranous septum. The present study shows that although anatomic evidence of partial closure was present in two fifths of the hearts studied, only rarely was it due to so-called aneurysm of the membranous septum.

It is now well accepted that a good proportion of defects in the ventricular septum occurring in otherwise normal hearts close spontaneously or at least diminish in size sufficiently that they do not constitute a threat to the patient. Hoffman[1–3] has estimated that 40% of defects present at birth will close during the first 2 years of life and that three fifths will close by age 5 years. Small defects are more likely to close than large ones. It also has been suggested that defects in the membranous septum are less likely to close than are those elsewhere in the septum.[4] Defects abutting on the membranous septum also diminish in size or close by formation of an "aneurysm of the membranous septum."[5–7] In the last of these studies, Freedom et al[7] acknowledged that in many cases, if not most, the tissue closing the defect was not derived from the membranous septum, but rather from tricuspid valve leaflets. This finding was also shown by the well-illustrated study of Chesler et al.[8] Because of the wide acceptance of the term *aneurysm of the membranous septum* and the failure to differentiate alternate mechanisms by angiocardiographic investigation, Freedom et al[7] continued to use the term, although they compromised by adding "so-called" to their title. It now seems that cross-sectional echocardiography will provide the tool for distinction of these various mechanisms which may reduce the size of a perimembranous ventricular septal defect (VSD). Therefore, it becomes necessary to know more precisely the morphologic characteristics and origin of the structures that produce the diminution in size. With this in mind, we examined the unoperated hearts with isolated VSD in the Museum of Children's Hospital of Pittsburgh.

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Material and Methods

All otherwise normal hearts having VSD were examined. Hearts with muscular or doubly committed subarterial defects with muscular posteroinferior rims were excluded. There remained 69 hearts having an isolated VSD in which the part of the central fibrous body formed by fibrous continuity between the tricuspid and aortic valves (the atrioventricular component of the membranous septum) constituted a border of the defect. Such defects are usually referred to as "membranous" VSDs. However, because the membranous septum may actually be present in such hearts and because there is

TABLE I Closure of Perimembranous Ventricular Septal Defect: Mechanism of Closure

Type of Defect	n	Nil	TV Leaflet	TV Tags	Subaortic Tags	Prolapse	Percent With Closure
Inlet	17	9	2	5	1	0	47
Trabecular	23	8	3	10	1	1	65
Outlet	20	20	0	0	0	0	0
Confluent	9	6	1	1*	0	2	33
Total	69	43	6	16	2	3	38

* One defect had both tags and prolapse.
TV = tricuspid valve.

almost always a defect in the muscular septum adjacent to the membranous septum, "perimembranous" seems a more precise term. These perimembranous defects were then examined to determine the direction of their extension into the muscular septum. On this basis, the defects were divided into inlet, trabecular or outlet types, depending on whether the defect occupied predominately the parts of the inlet, trabecular, or outlet muscular septum adjacent to the central fibrous body.[9]

Some defects were considered to extend into all 3 parts of the muscular septum, and these were designated "confluent" defects. All defects were then examined from the right ventricular aspect to see if their size was diminished by any anatomic structures. In each case the left ventricular aspect was examined to determine if there was any remnant of the interventricular component of the membranous septum present, and if this contributed to closure.

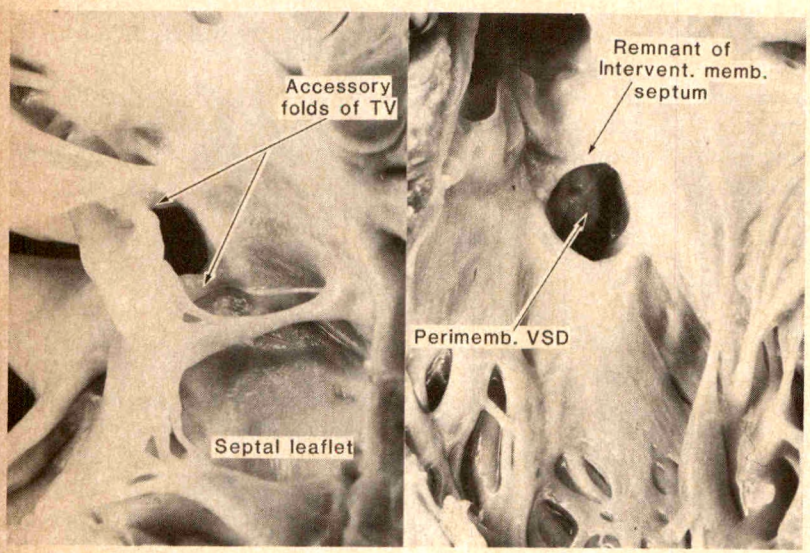

FIGURE 1. Left, the right ventricular aspect of a small perimembranous trabecular ventricular septal defect (VSD) in which the size is reduced by membranes derived from the tricuspid leaflet tissue. **Right,** the left ventricular aspect shows that the membranes are distinct from the remnant of the interventricular component of the membranous septum. TV = tricuspid valve.

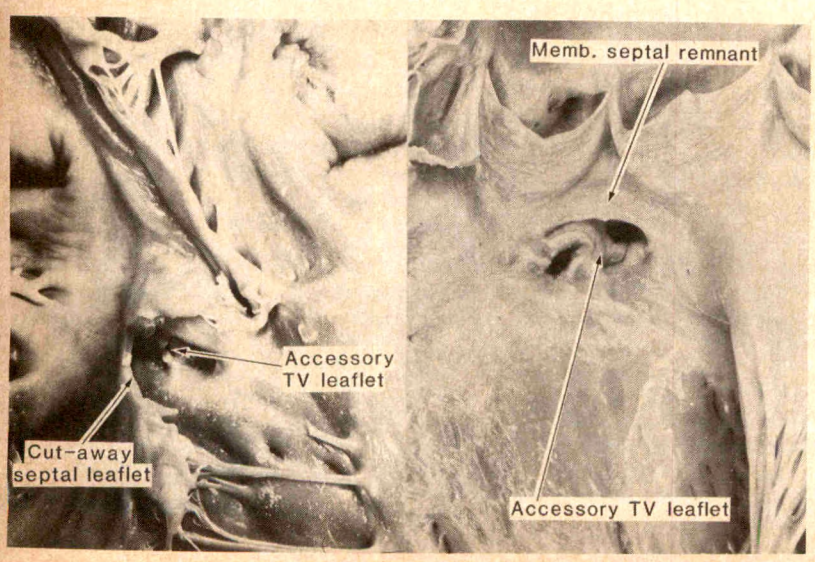

FIGURE 2. A large perimembranous septal defect almost closed by membranes, similar to those shown in Figure 1. **Right,** the left ventricular aspect again shows the remnant of the interventricular membranous septum. The folds are also discrete from the septal leaflet of the tricuspid valve (TV), which has been cut away in the **left panel.**

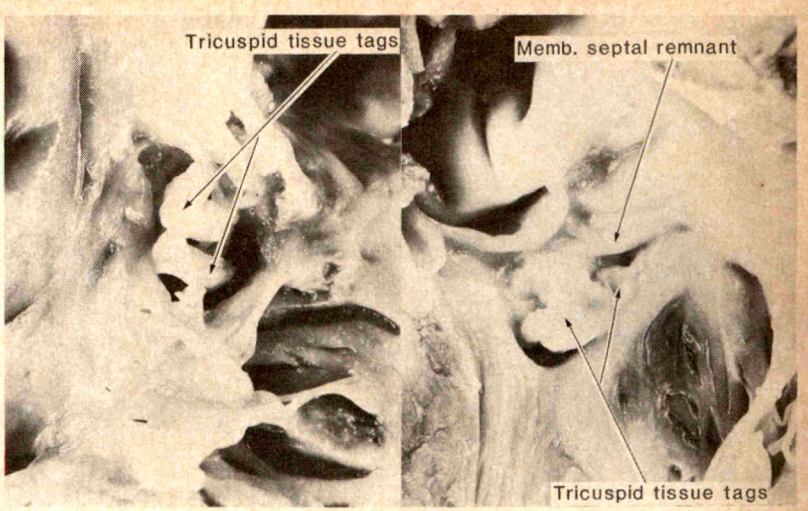

FIGURE 3. A perimembranous trabecular defect which is partially closed by grape-like tags derived from the tricuspid valve leaflets. The right ventricular (**left panel**) and left ventricular (**right panel**) aspects are shown.

Results

Of the 69 hearts examined, 26 (38%) showed anatomic evidence of diminution in size of the defect. Only 2 were completely closed, both of these by adherence of the septal leaflet of the tricuspid valve to the margin of a trabecular defect. In 24 hearts there was partial closure.

Seventeen of the 69 defects were of the inlet type and nearly half of these were partially closed. Twenty-three hearts had perimembranous defects largely confined to the trabecular septum, and two thirds of these were diminished in size. Twenty defects extended into the outlet septum and none of these showed evidence of closure. The remaining 9 hearts had confluent defects, and one third were reduced in size by discrete anatomic lesions.

The structures producing closure are listed in Table I. The majority were derived from reduplications of tricuspid valve leaflet tissue. In some cases these reduplications simply produced folds in the posterosuperior and posteroinferior quadrants of the defect (Fig. 1). These folds were discrete from the interventricular component of the membranous septum and in 3 cases produced almost complete closure (Fig. 2). In other hearts the reduplications were dysplastic and pouch-like and significantly diminished the size of the defect (Fig. 3). Sometimes the pouches were tethered by chordae tendineae both to the septal crest and to the tricuspid valve leaflets. All of these pouches were separate from the remnant of the interventricular membranous septum.

The second most common arrangement was attachment of leaflets of the tricuspid valve across the defect. In 2 hearts this arrangement produced complete closure and in another virtually complete closure of the defect (Fig. 4). In 1 heart with a confluent defect the partial closure produced by a dysplastic tricuspid valve leaflet was enhanced by prolapse of the noncoronary and right coronary leaflets of the aortic valve (Fig. 5). Prolapsed aortic valve leaflets reduced the size of the defect in 2 other hearts with trabecular and confluent defects, respectively.

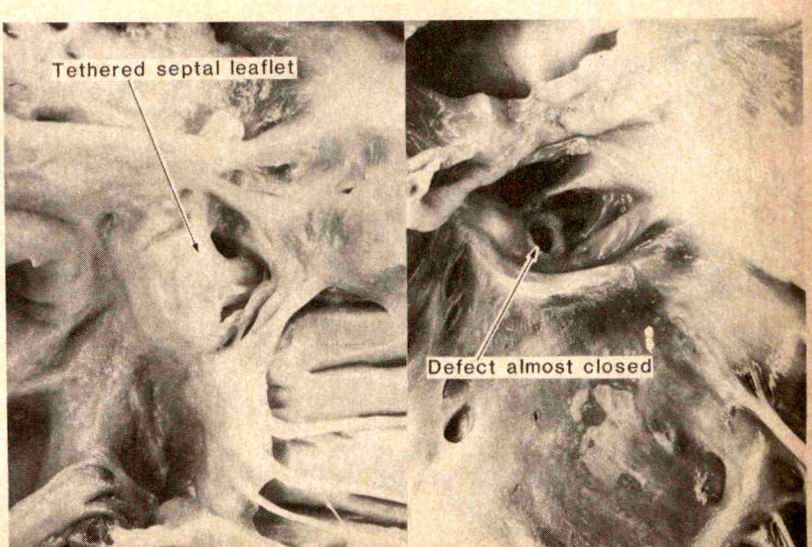

FIGURE 4. The right ventricular (**left panel**) and left ventricular (**right panel**) aspects of a perimembranous trabecular defect almost closed by adhesion of the septal leaflet of the tricuspid valve.

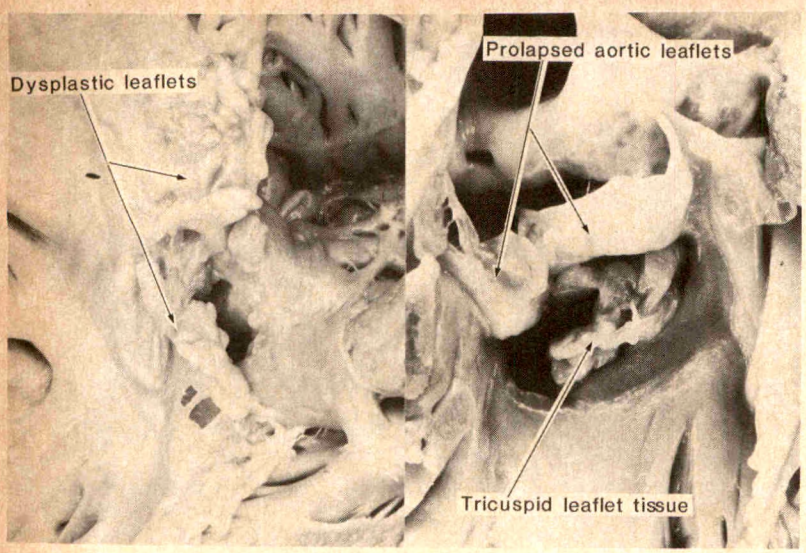

FIGURE 5. A perimembranous trabecular defect in which size is diminished in part by dysplastic conversion of the tricuspid valve leaflet (**left panel**) and in part by prolapse of the right and noncoronary aortic valve leaflets (**right panel**).

Lesions that may have originated from the interventricular component of the membranous septum were found in only 2 hearts, 1 with an inlet and the other with a trabecular defect. In 1 of these a grape-like expansion of fibrous tissue originated from the aortic root beneath the left coronary aortic valve leaflet and was tethered to the septum by chordae. A small protuberant and thickened membranous septal remnant hung in the roof of the defect medial to this structure. The predominant effect of these lesions was to produce subaortic outflow tract obstruction (Fig. 6), but there was narrowing of the VSD as well. In the second heart a long-sac like structure in the anticipated site of the interventricular membranous septum was attached by long chordae to the muscular septum, and both reduced the size of the VSD and produced subaortic obstruction (Fig. 7).

Discussion

Although Varghese et al[5,6] promoted "aneurysm of the membranous septum" as a mechanism for closure of perimembranous VSD, the larger study by Freedom et al[7] from the same institution showed that it was unlikely that the closing tissue was derived from the interventricular component of the membranous septum or its remnant. This conclusion had already been reached by Chesler et al[8] from observations on a small series of hearts. Examination of our larger series of hearts simply serves to confirm these observations. In most cases the tissue partially or completely occluding the defect is either a tricuspid valve leaflet itself or extrusion of folds of tissue from the ventricular aspect of the valve leaflets in the environs of the defect. These folds are closely related to the interventricular compo-

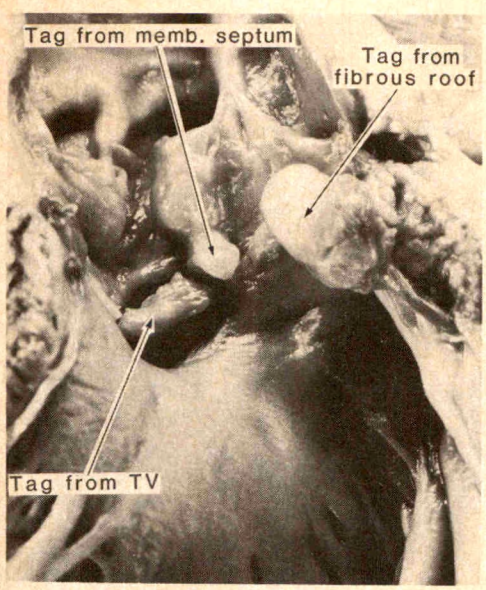

FIGURE 6. A heart with a small perimembranous trabecular defect with 3 subaortic tissue tags derived from the tricuspid valve leaflet (TV), the remnant of the interventricular membranous septum and the subaortic fibrous root. Note that the membranous remnant tag is the smallest of the 3.

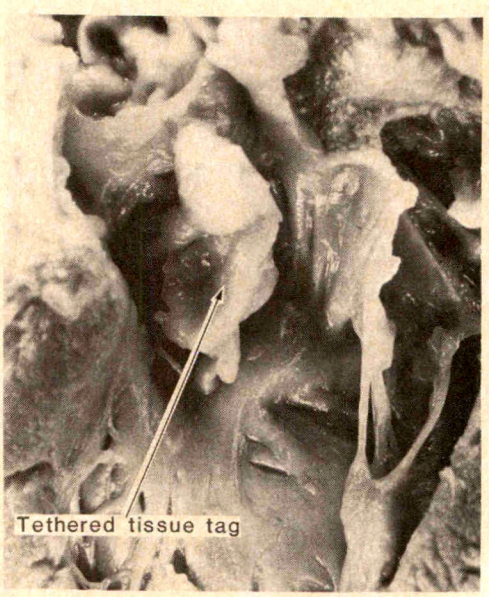

FIGURE 7. Another heart with a perimembranous defect partially blocked by an extensive sac-like aneurysm which originates from the site of the remnant of the interventricular membranous septum. The tissue tag considerably narrows the left ventricular outflow tract.

nent of the membranous septum when the latter structure is present, but they are discrete from it. In 2 hearts grape-like lesions originated from a remnant of the membranous septum and obstructed the subaortic outflow tract as well as narrowed the VSD. It may be significant that in other situations in which such fibrous tissue tags are found originating from membranous septal remnants, they too produce outflow tract obstruction rather than closure of a VSD. Examples are the tissue tags found in complete[10] and corrected[11] transposition and in atrioventricular septal defects ("endocardial cushion defects").[12,13] Although these tags are often said to be derived from endocardial cushion tissue,[7,12] we know of no work, experimental or otherwise, to substantiate this statement. We cannot be sure that these lesions originated from the membranous septum, but we cannot identify any other tissue as their source. It is probably most accurate to describe them simply as subaortic tissue tags.

In 3 cases prolapsed aortic valve leaflets reduced the defect size, a mechanism described by Moss and Siassi.[14] We also encountered a case clinically in which a VSD murmur disappeared synchronously with the appearance of a murmur of aortic regurgitation.

When Freedom et al[7] discussed their use of the term *aneurysm of the membranous septum*, they justified it by common usage, inability to distinguish the anatomy in a clinical setting, and lack of a superior term. We would suggest that cross-sectional echocardiography now provides the means of distinguishing the different lesions which diminish the size of perimembranous VSDs. Simple descriptive terms account for their categorization. Thus, in our series diminution in size was produced either by an adherent tricuspid valve leaflet, tricuspid leaflet tissue tags, subaortic tissue tags, prolapsed aortic valve leaflets, or a combination of these. Our study also showed that nearly two fifths of perimembranous VSDs had some signs of closure. These figures must be treated with caution because they are obtained from an autopsy series. We obviously cannot be sure that the partial occlusion demonstrated in these hearts was part of a dynamic process which would have led to complete closure had the child survived long enough. However, the fact that none of the outlet perimembranous defects showed signs of closure is surely significant, substantiating Somerville's concept[15] that the position of a perimembranous defect within the septum is just as important in its natural history as the fact that it is subaortic and abuts directly on the central fibrous body.

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2-Dimensional Echocardiographic Appearance of Complete Left-Sided Juxtaposition of the Atrial Appendages

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This report describes the 2-dimensional (2-D) echocardiographic appearance of left-sided juxtaposition of the atrial appendages (JAA). From January 1, 1978, to June 30, 1979, 2 infants had the diagnosis of left-sided JAA at autopsy. Both patients had previously been examined by subxiphoid 2-D echocardiography. On review of these studies, the septum secundum was found to be oriented posteriorly in the transverse view of the atria. From July 1979 to June 1981, prospective evaluation of all infants for the presence of this finding revealed 2 more patients. Left-sided JAA was confirmed at surgery in 1 case and by selective right atrial angiography in the other. The diagnosis of left-sided JAA has important implications for both atrial baffle operations and for the Fontan procedure.

Left-sided juxtaposition of the atrial appendages (JAA) is an unusual anomaly typically associated with several types of conotruncal malformations: d-transposition of the great arteries, some varieties of double-outlet right ventricle, and anatomically corrected malposition.[1–5] It may occur in complete or partial form[2,6,7] and frequently coexists with hypoplasia of the tricuspid valve and right ventricular sinus. It is particularly increased in frequency among patients with the {S,D,L} segmental combination.[8] Several reports have described the angiographic diagnosis of JAA.[9–11] This report presents the 2-dimensional (2-D) echocardiographic appearance of left-sided JAA and discusses the surgical implications of this diagnosis.

Methods

From January 1, 1978 to June 30, 1979, the diagnosis of left-sided JAA was made at autopsy in 2 infants. Both had been examined by 2-D echocardiography at the Children's Hospital Medical Center, Boston. From July 1, 1979 to June 30, 1981, all patients <2 years old who were examined by 2-D echocardiography were prospectively evaluated for left-sided JAA. All 2-D echocardiographic examinations were performed from the subxiphoid region with a Picker Echoview 80 CI system, using either a 5-MHz short-focus (active element diameter 13 mm) or 3.5-MHz medium-focus (active element diameter 13 mm) crystal. The transverse echocardiographic plane used is shown in Figure 1.

Results

In the retrospective examination of the 2-D echocardiograms of the first 2 patients, the atrial appendages themselves were convincingly exhibited in only 1 patient. However, we discovered 1 unusual finding common to both cases: in the transverse view of the atria, the septum secundum was deviated posteriorly (Fig. 2A). The orientation of the septum primum in these 2 patients was normal. From July 1979 to June 1981, prospective examination of all infants for the presence of an abnormally posteriorly deviated septum secundum revealed 2 further patients with this feature. Left-sided JAA was subsequently confirmed at surgery in 1 and by selective right atrial angiography in the other. The true incidence of false-negative diagnosis based on the orientation of the septum secundum is unknown, since a significant number of infants undergoing 2-D echocardiography never undergo further investigation. However, of the 480 infants during the study with a normally oriented septum secundum who did have subsequent cardiac catheterization, surgery, or autopsy, none was diagnosed as having left-sided JAA.

Discussion

Although several investigators have described the angiographic diagnosis of JAA;[10,11] there have not been

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Address for reprints: Alvin J. Chin, MD, Department of Cardiology, Children's Hospital Medical Center, 300 Longwood Avenue, Boston, Massachusetts 02115.

any reports of the 2-D echocardiographic appearance of this anomaly. The atrial appendages themselves are often difficult to display because of their tortuosity and their apposition to the lungs. Although the left atrial appendage can be imaged in some patients, the right atrial appendage is especially difficult to identify consistently, and it is the right atrial appendage which is displaced in left-sided JAA. However, the qualitative assessment of septum secundum orientation in the transverse view of the atria appears to be a reliable test for the presence of left-sided JAA.

Examination of both autopsy cases revealed that the septum secundum was deviated posteriorly and leftward, as was its external counterpart, the superior-most aspect of the interatrial fold (Fig. 3). It is thus not surprising that the transverse view of the atria (Fig. 1) shows this deviation so clearly.

Two thirds of reported cases with left-sided JAA have d-transposition of the great arteries[1–7,9–12] and would be expected to undergo balloon atrial septostomy. In patients with left-sided JAA, the septostomy catheter may appear by fluoroscopy to be in the left atrium when it is, in fact, in the levo-posed right atrial appendage.[10,12] Inflating the balloon of the septostomy catheter in the right atrial appendage and pull back could result in eversion of the appendage or rupture of the right atrium. Precatheterization knowledge of the presence of JAA alerts the cardiologists to this potential hazard; 2-D echocardiography can also be used to confirm catheter position before performing balloon septostomy.[13]

The presence of left-sided JAA may alter surgical management of certain associated lesions. First, in cases of double-outlet right ventricle or d-transposition of the great arteries where there is atresia or hypoplasia of the tricuspid valve, physiologic surgical repair may involve a right atrial–pulmonary artery conduit or direct anastomosis. In patients with d-malposed great vessels, left-sided JAA places the levo-posed right atrial appendage adjacent to the main pulmonary artery. Awareness of the presence of left-sided JAA alerts the surgeon to the technical feasibility of fashioning a patulous side-to-side anastomosis between the right atrial appendage and the main pulmonary artery. In the face of early reports of conduit obstruction after the Fontan procedure,[14,15] a direct right atrial–pulmonary artery anastomosis, rendering an artificial conduit unnecessary, appears to be an increasingly attractive

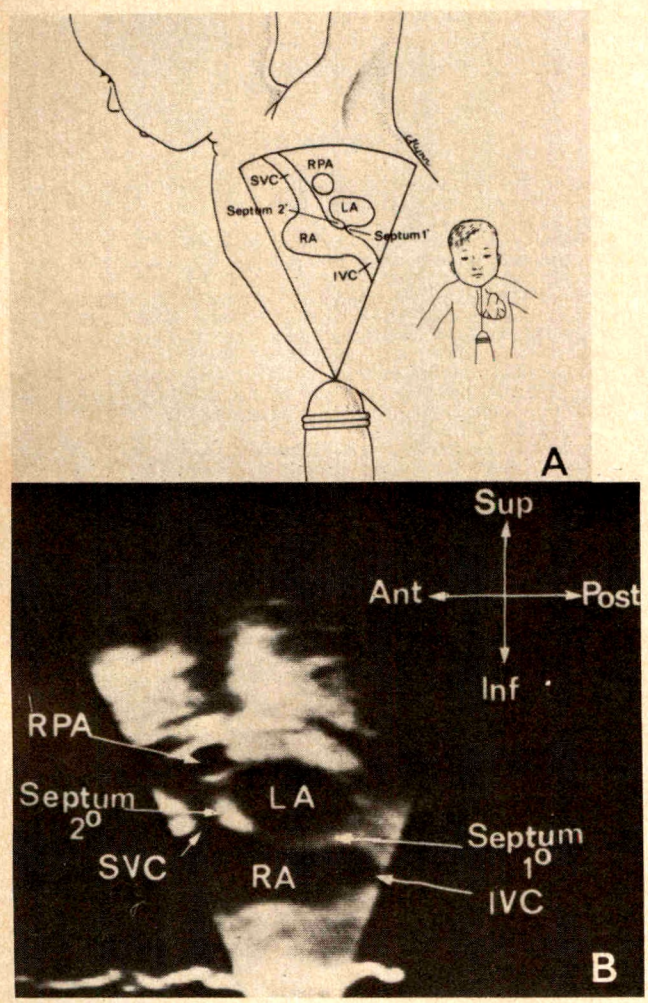

FIGURE 1. A, ultrasound plane used to obtain the transverse view of the atria. IVC = inferior vena cava; LA = left atrium; RA = right atrium; RPA = right pulmonary artery; SVC = superior vena cava; septum 1° = septum primum; septum 2° = septum secundum. **B,** 2-dimensional echocardiogram of normal patient, transverse view of the atria. Ant = anterior; Inf = inferior; Post = posterior; Sup = superior.

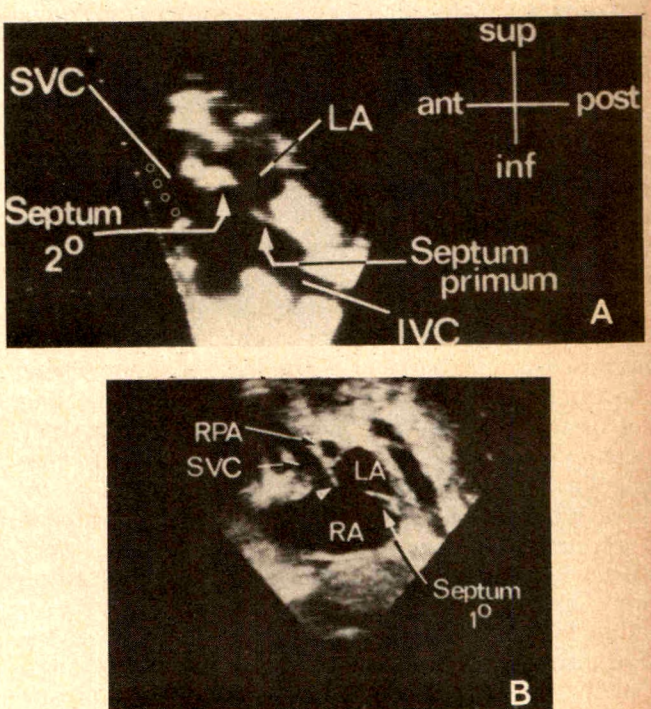

FIGURE 2. A, 2-dimensional echocardiogram of patient with complete left-sided justaposition of the atrial appendages, transverse view of the atria. The septum secundum (2°) is deviated posteriorly. An atrial septal defect is present. **Open circles** outline the anterior margin of the superior vena cava. **B,** 2-dimensional echocardiogram of a patient with a secundum atrial septal defect but without juxtaposition of the atrial appendage transverse view of the atria. Note the absence of any posterior deviation of the septum secundum (**white arrowhead**). Abbreviations as in Figure 1.

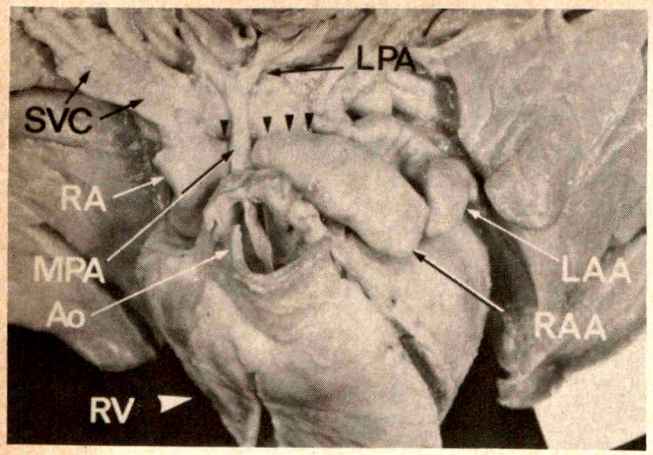

FIGURE 3. Autopsy specimen (external superior view) of the patient whose echocardiogram is shown in Figure 2A. The external counterpart of the septum secundum, the interatrial fold (**black arrowheads**), is deviated leftward and posteriorly in complete left-sided juxtaposition of the atrial appendages. This patient had double-outlet right ventricle with pulmonary atresia, atrioventricular canal–type ventricular septal defect, secundum atrial septal defect, and large patent ductus arteriosus. The right atrial appendage (RAA) is levo-posed through the transverse sinus posterior to the great arteries. Ao = aorta; LAA = left atrial appendage; LPA = left pulmonary artery; MPA = main pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

surgical technique. Second, the Blalock-Hanlon procedure appears to be technically more demanding in patients with left-sided JAA. Rosenquist et al[7] noted that the part of the right atrium between the interatrial groove and the atrioventricular sulcus is smaller than normal, making the placement of a vascular clamp hazardous. Open atrial septectomy may be the safer technique in patients with left-sided JAA. Third, atrial baffle operations such as the Mustard and Senning procedures pose special problems in patients with left-sided JAA. Just as for the Blalock-Hanlon procedure, the major complicating feature appears to be the "small right atrial cavity size."[16] We believe that the right atrium appears small in complete left-sided JAA because the only portions of the right atrium between the interatrial groove and the right atrioventricular sulcus are the sinus venosus component and the small portion contributed by the right half of the atrioventricular canal. The primitive atrium component including the right atrial appendage is levo-posed through the transverse sinus posterior to the great arteries (Fig. 3). To deal with the small right atrium in Mustard repair, Urban et al[16] suggested extending the right atriotomy incision across the interatrial groove between the right upper and lower pulmonary veins and inserting a Dacron® patch to enlarge the pulmonary venous atrium (neo–left atrium). Although so far only Mustard repairs[16,17] have been reported in patients with left-sided JAA, we anticipate that an analogous enlargement of the neo–left atrium during the Senning repair would also be required.

Two-dimensional echocardiography affords an opportunity to examine the in vivo spatial relations of cardiac structures and can frequently offer new insight regarding the possible embryologic basis of complex cardiac anomalies. The posterior displacement of the septum secundum together with the posterior and leftward displacement of the right atrial appendage suggested a possible explanation of the morphogenesis of this condition. It is possible in this lesion that during embryogenesis the primitive atrium, whose only derivatives are the septum secundum and the atrial appendages, becomes malaligned with respect to the sinus venosus. The possibility of malalignment of cardiac segments with respect to one another may explain many cardiac anomalies[18]; for example, there is a spectrum of alignment of the common atrioventricular valve vis-a-vis the ventricles in complete common atrioventricular canal.[19] Similarly, the degree of malalignment between the primitive atrium and the sinus venosus may thus determine whether there is partial or complete juxtaposition of the atrial appendages. Finally, the theory that abnormal septum secundum orientation is associated with JAA predicts that the septum secundum should be deviated rightward and anteriorly in right-sided JAA.

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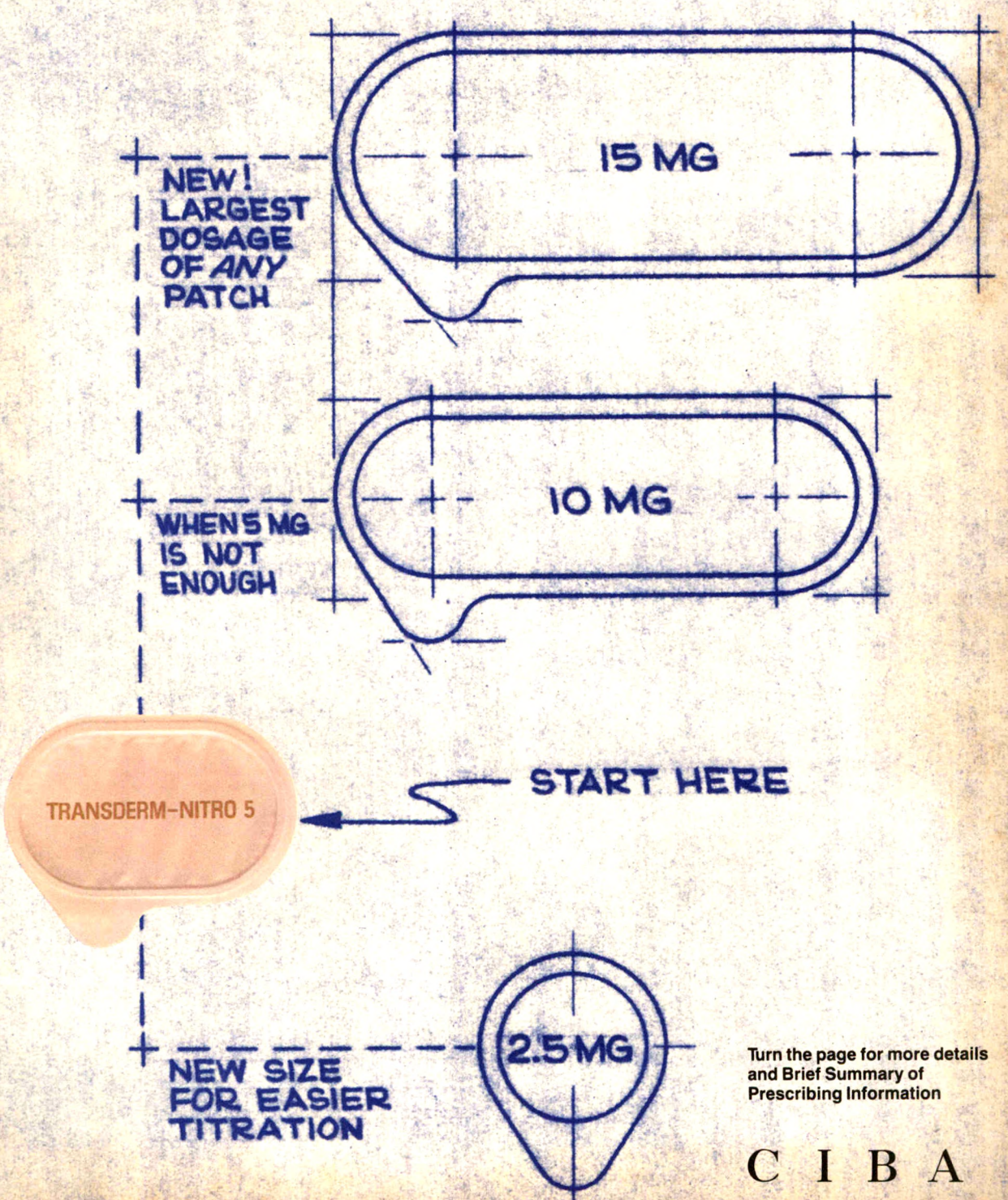

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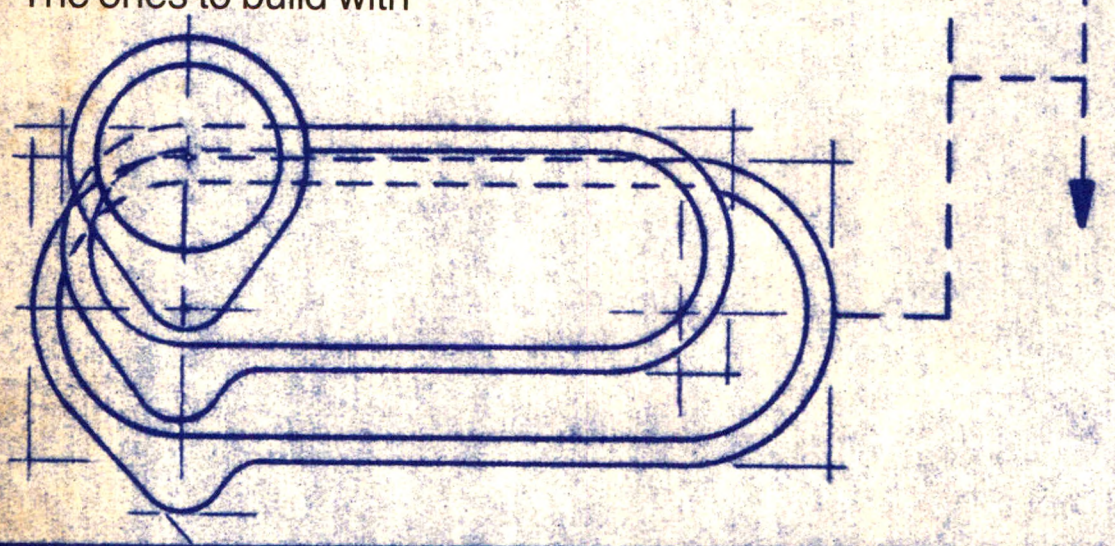

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Growth and Tissue Abnormalities in Young People With Cyanotic Congenital Heart Disease Receiving Systemic–Pulmonary Artery Shunts

DAVID BAUM, MD, REBECCA Q. BECK, MA, and WILLIAM L. HASKELL, PhD

The effects of systemic–pulmonary artery shunts on growth, body composition, and adipose tissue were studied in 29 children, aged 2 to 16 years, with cyanotic congenital heart disease. Of these, 16 received surgical shunts and 13 were unoperated. Postoperatively, all patients who received shunts were better oxygenated (systemic oxygen saturation 69 ± 11% preoperatively and 84 ± 4% postoperatively; mean ± standard error of the mean) and were symptomatically improved. However, the groups were not significantly different in height, weight, lean body mass, total body fat, lean/fat ratio, cellular lipid content, or total number of lipid-containing fat cells. Age at operation did not seem to influence the effects of surgery. These observations suggest that growth and certain measurements of tissue development were unaffected by surgical systemic–pulmonary artery shunts despite increased oxygenation and symptomatic improvement after operation.

Young persons with cyanotic congenital heart disease are short and underweight.[1–3] They have reduced lean and fat tissues. The reduction in adipose tissue seems largely the result of a subnormal number of lipid-containing fat cells rather than diminished cellular lipid content.[1] While there is general agreement that height and weight are reduced in cyanotic patients with reduced pulmonary blood flow, there is less agreement concerning the rate of growth and weight gain after systemic–pulmonary artery shunts.[1,3–6] Regardless of whether growth and weight gain are accelerated after palliation, patients remain undersized and underweight despite improvement in oxygenation.[1,3–6] The tissue abnormalities that contribute to these disorders in surgically shunted cyanotic children are unknown. This study was performed to determine the fat and lean tissue changes associated with poor growth and weight gain in such patients.

Methods

Children aged 2 to 16 years at the time of cardiac catheterization were studied. All had cyanotic congenital heart disease and reduced pulmonary blood flow. Patients born prematurely or with metabolic disease, chromosomal aberrations, or other significant noncardiac congenital defects were excluded.

Thirteen unoperated patients (5 girls, 8 boys) comprised 1 group. The second group included 16 young persons (3 girls, 13 boys) who received palliative surgery consisting of a Blalock-Taussig (n = 11), Potts (n = 2), or Waterston (n = 3) anastomosis. Although height, weight, and adipose and lean tissue mass were determined longitudinally, tissue studies were performed only at the time of cardiac catheterization. In patients 2 to 14 years of age, lean and fat tissue mass were derived by the Friis-Hansen method.[7] Hydrostatic weighing[8] was used for those >14 years of age. For cellular studies, small adipose samples were obtained through the groin incision made for percutaneous catheter introduction. Fat cell size (cellular lipid content) and total number of lipid-containing adipocytes were determined.[9] When available, height and weight of the parents also were recorded.

Group comparisons of height, weight, lean body mass, total body fat, lean/fat ratio, cellular lipid content, and total number of lipid-containing adipocytes were performed using the analysis of variance (BMD computer program). A Student *t* test was used to determine the significance of the difference between 2 means. P values <0.05 were considered significant.

Results

Patients: The most common cardiac anomaly in both groups was tetralogy of Fallot (20 of 29 patients). Six had complex cyanotic heart disease, 2 double-outlet right ventricle and pulmonary stenosis, and 1 transpo-

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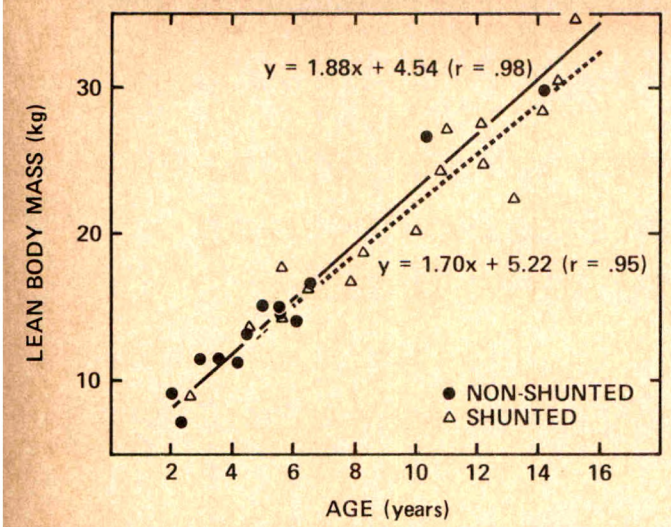

FIGURE 1. Lean body mass in shunted and nonshunted children with cyanotic congenital heart disease. Regression lines and correlation coefficients are shown.

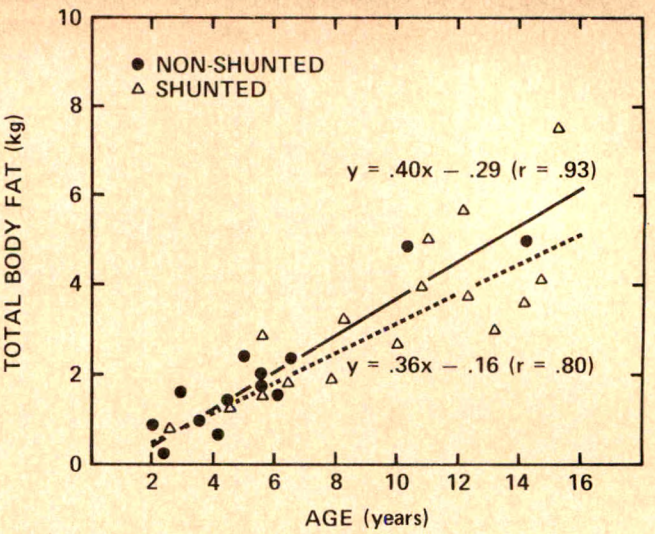

FIGURE 2. Total body fat in shunted and nonshunted children with cyanotic congenital heart disease. Regression lines and correlation coefficients are shown.

sition, ventricular defect, and pulmonary stenosis. All children were cyanotic in the first year of life. Oxygen saturation in the nonoperated patients was 77.7 ± 6.0% (mean ± standard error of the mean [SEM]).

Surgical decisions were based upon symptoms, degree of hypoxemia, complexity of cardiac anomalies, size, and age. In patients who received palliative surgery, preoperative oxygen saturation was 68.8 ± 11.2% and postoperative saturation was 83.6 ± 4.0%. All children who received a shunt had improvement in symptoms. Age at operation was 3.2 ± 3.5 years (range 0.01 to 9.4). Seven of the 16 palliated patients were operated upon before age 0.7 years, with 4 in the first month of life. Of those operated upon very early, arterial oxygen saturation increased from 63.7 ± 12.8% to 82.7 ± 3.5%.

Height and weight: Comparison of the 2 groups of patients revealed no difference in height or weight. When these data were expressed as the percentiles of the general American population,[10] height and weight of the 2 groups again were not significantly different. In the group receiving surgery, there were no significant differences in pre- and postoperative height and weight percentiles. Furthermore, in operated patients in whom sufficient data were available, there was no apparent difference in the pre- and postoperative rates of growth and weight gain. At the time of cardiac catheterization, the patients' height and weight, expressed as percentiles, were compared with those of their parents.[11] Unoperated children were shorter ($p < 0.01$) than their mothers and both shorter ($p < 0.01$) and lighter ($p < 0.025$) than their fathers. Palliated patients were lighter ($p < 0.025$) than their mothers but both shorter ($p < 0.01$) and lighter ($p < 0.01$) than their fathers.

Tissue analyses: Lean and adipose tissue mass in the shunted group was not significantly different from those of the nonshunted group (Fig. 1 and 2). In those operated patients with sufficient pre- and postoperative data to allow comparison, palliative surgery produced no difference. To learn whether palliative surgery produced a proportional change in body composition, lean/fat ratios in the 2 cyanotic groups were compared. Since there was no significant difference in the ratios (Fig. 3), it appeared that palliation did not alter the fat and lean tissue contributions to the hypoxemia-induced decrease in body weight.

Neither cellular lipid content (Fig. 4) nor number of lipid-containing fat cells (Fig. 5) was significantly different in operated and nonoperated patients.

Discussion

Despite improved oxygenation and symptomatic relief, our patients' growth and weight gain were not improved after systemic–pulmonary artery shunts. Similarly, the relative contributions of fat and lean tissue components to their underweight were not af-

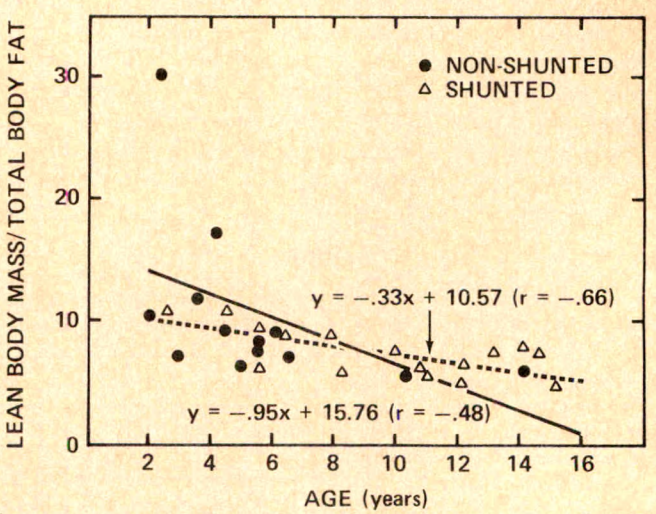

FIGURE 3. Lean/fat ratio in shunted and nonshunted children with cyanotic congenital heart disease. Regression lines and correlation coefficients are shown.

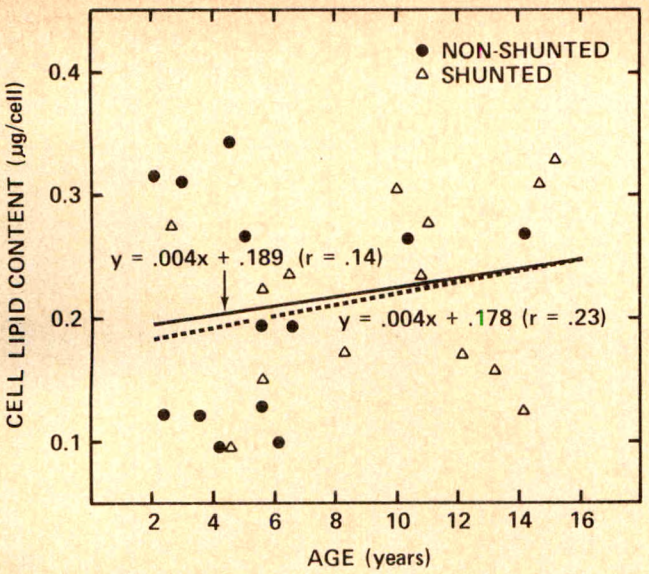

FIGURE 4. Cell lipid content in shunted and nonshunted children with cyanotic congenital heart disease. Regression lines and correlation coefficients are shown.

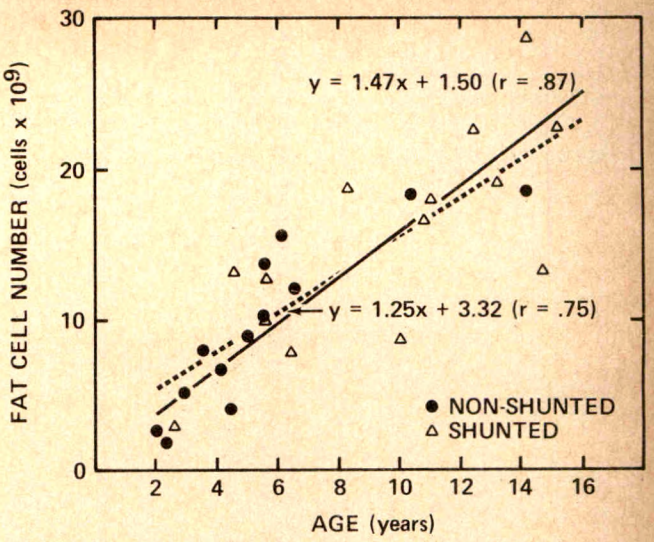

FIGURE 5. Fat cell number in shunted and nonshunted children with cyanotic congenital heart disease. Regression lines and correlation coefficients are shown.

fected. These conclusions were made because height, weight, lean and fat tissues, and lean/fat ratios in unoperated and postoperative patients given palliative shunts were not significantly different. Further supporting this conclusion, the rates of growth, weight gain, and lean and fat tissue change seemed no different before and after operation. Although preoperative arterial oxygen saturations in operated children were lower than arterial oxygen saturations in nonoperated children, we believe that our comparisons were valid for 2 reasons. First, there was a subgroup of shunted children with only a very brief period of severe hypoxemia. In this subgroup, 7 palliated infants were operated upon before age 0.7 year, with 4 in the first month of life. Yet there were no growth differences between children operated upon before 0.7 year and those shunted later. Neither differed from nonoperated patients. Second, postoperative arterial oxygen saturations were greater than oxygen saturations of nonshunted patients. As a result, over the course of their illness, hypoxemia was less of a handicap to operated than unoperated children.

There are several reasons why growth and weight gain may not improve postoperatively. Although oxygenation is increased, it is still subnormal. The original congenital heart disease remains and, in fact, palliative surgery imposes an additional left-to-right shunt. Thus, cardiopulmonary work remains abnormally high.[12] As long as the children continue to be underweight, the ratio of surface area to body weight is high and, as a result, heat loss is facilitated.[13] Finally, palliated children often continue to eat poorly and there is reason to believe that gastrointestinal absorption may be impaired.[14] Therefore, substrate needs, including that of oxygen, are greater than normal, while substrate availability is decreased. This combination of circumstances results in less residual substrate for storage and growth.

Children with successful palliative shunts often benefit from the surgery. With increased pulmonary blood flow, oxygenation is improved and polycythemia decreased. Activity is increased, symptoms are relieved, and hypoxic spells may cease. Nevertheless, growth failure continues. Reduction in weight, adipose tissue mass, and number of lipid-laden cells and decreased height and lean tissue suggest a widespread structural abnormality. Since structural abnormality is often associated with functional disorders, the described tissue abnormalities in cyanotic patients may portend disordered cellular function.

Structural and functional derangements of adipose tissue as well as secondary changes involving other organs may be important.[15,16] Such tissue changes may reach a stage when they become irreversible. While there is evidence suggesting that adipose tissue abnormalities produced in young animals are not fully reversible,[17,18] whether such irreversibility occurs in man is not known. Undoubtedly, factors such as symptoms, age, and size still remain the primary considerations in the surgical decision. However, if there is a stage in the young developing child when hypoxemia-induced tissue defects become irreversible, the limited growth benefits of palliative shunting deserve attention in planning long-term management.

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The Marfan Syndrome in Early Childhood: Analysis of 15 Patients Diagnosed at Less Than 4 Years of Age

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The clinical, cardiac and echocardiographic features were reviewed of 15 consecutive infants and children with the Marfan syndrome who presented at <4 years of age. The 10 females and 5 males were diagnosed at a mean age of 18 months (range 2 days to 3.5 years); 13 were followed up for a mean of 45 months (range 8 to 109 months) and 2 were lost to follow-up. On first evaluation, 5 patients had mitral regurgitation (MR) and none had aortic regurgitation (AR). Echocardiography showed aortic root dilatation in 9 and mitral valve prolapse (MVP) in 9; only 2 patients had a normal echocardiogram. At follow-up examination, all patients had aortic root dilatation; the rate of increase in aortic root diameter was generally greater than predicted on the basis of body surface area. One patient had AR at age 10 years. All 13 patients had MVP; 9 had progressive mitral valve dysfunction and 4 had mitral valve replacement. One patient died immediately postoperatively. Thus, aortic root dilatation is usually present in early childhood and serves as an objective indicator of the Marfan syndrome. MVP is common and MR, which may require valve replacement, is the leading cause of cardiovascular morbidity in childhood. Echocardiography is useful in the diagnosis and routine management of infants and children in whom the Marfan syndrome is suspected.

The Marfan syndrome is a heritable disorder of connective tissue in which the most prominent abnormalities occur in the skeletal, ocular, pulmonary, and cardiovascular systems.[1–4] Skeletal features were described in 1896[5] and mitral valve dysfunction was first noted in a patient with arachnodactyly in 1912.[6] Many years later, cardiovascular features were recognized as integral to the syndrome. Aortic dilatation[7] and dissection[8] were reported in 1943 and fragmentation and disarray of elastic fibers in the aortic media were noted. This histopathology, called cystic medial necrosis, also occurs in other connective tissue disorders[9] and in association with hypertension and aging.[10] Early surveys of cardiovascular involvement in the Marfan syndrome focused on diagnosis by auscultation or postmortem examination.[11,12] Estimates of frequency of abnormalities ranged from 40 to 60% of adults in these studies.

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Appreciation of frequency and kind of cardiovascular features in patients with Marfan syndrome was greatly altered by the introduction of echocardiography. Several surveys of adults and children detected mitral valve prolapse (MVP), aortic dilatation or both in about 95%.[2,13–15] In the studies reported here, we analyzed clinical and echocardiographic findings in children <4 years of age who met strict criteria for the diagnosis of Marfan syndrome and were evaluated consecutively in 1 clinic, to determine the frequency, severity, and natural history of their cardiovascular abnormalities.

Methods

The medical records of all patients with the Marfan syndrome <4 years of age who were evaluated between 1970 and 1982 in the Medical Genetics Clinic were reviewed. Diagnosis of the Marfan syndrome was based on skeletal, ocular, and cardiovascular features and family history.[2] All subjects underwent echocardiography, but in no case were the results used in establishing the diagnosis. The study included 5 boys and 10 girls who presented at 2 days to 3½ years of age (mean 18 months). This group comprised about 9% of all patients <22 years old affected by the Marfan syndrome evaluated at our institution during the same period. Seven patients had a parent affected by the Marfan syndrome; the other 8 had a negative family history for connective tissue disorders. Examination and echocardiography of their parents did not re-

TABLE I Clinical Characteristics of the 15 Patients

Case	Age (mo) 1st Visit	Age (mo) Latest Visit	Height (cm) 1st Visit	Height (cm) Latest Visit	Weight (kg) 1st Visit	Weight (kg) Latest Visit	Family History	Skeletal Features	Ocular Features
				Females					
1	2.5	10.5	63	75	5	8	Neg	A,D,J,P	E,M
2	7	140	72	149	6	32	Neg	A,D,P	M
3	12	32	77	93	7	11	Neg	A,J,P	M
4	28	70	94	105	14	15	Fa*	J,P	M
5	29	74	85	116	13	20	Neg	A,J	E,M
6	29	138	101	158	15	38	Neg	A,D,J,P	E,M
7	29	87.5	95	129	15	25	Fa	A,D,J,P	E,M
8	36	. . .	104	. . .	16	. . .	Fa	J	M
9	38	65	97	114	13	17	Neg	A,D	E,M
10	4	17	65	83	7	11	Moth	A,J	E
				Males					
11	0.07	39.5	52	99	4	16	Moth	A,D,J	Neg
12	12	37	83	93	9	13	Neg	J,P	E
13	13	45	84	100	10	17	Fa*	P	M
14	24	56	95	106	12	18	Neg	A	E
15	24	69	93	128	15	28	Fa	A,D,J,P	E,M

* Patients 4 and 13 are siblings.
A = arachnodactyly; D = dolichostenomelia; E = ectopia lentis; Fa = father; J = joint laxity; M = myopia; Moth = mother; Neg = negative; P = pectus deformity.

TABLE II Cardiovascular Characteristics of the Patients

Case	Age (mo)	BSA (m^2)	Auscultation Click	Auscultation Murmur	Auscultation MVP	Echocardiography ARD (cm)	LAD (cm)	LVDD (cm)	LVSD (cm)	PWT (cm)	VST (cm)
					Females						
1	2.5	0.31	0	MR	+	2.0	1.5	2.2	. . .	. . .	. . .
	11*	0.38	0	MR	+	2.2	1.8	4.1	3.2	0.7	0.6
2	42	.71	+	MR	+	1.8	1.8	4.2	3.0	0.5	0.5
	135	1.15	+	MR,AR	+	3.5	3.5	6.0	3.2	0.7	0.9
	140	1.23	+	AR	PMV	4.3	1.4	4.1	3.7	0.9	0.9
3	12	0.4	+	MR	+	1.9	2.2	3.7	2.0	0.5	0.4
	23		+	MR	+	2.0	4.1	5.5	3.1	0.6	0.9
	32	0.53	+	0	PMV	2.4	1.5	2.9	2.1	0.6	0.6
4	28	0.63	0	0	0	1.9	1.9	3.2	2.0	0.5	0.5
	70	0.89	+	0	+	2.6	2.1	4.0	2.6	0.6	0.6
5	29	0.64	0	0	0	2.2	1.2	3.0	1.8	0.5	0.5
	59	0.81	0	0	+	2.4	1.4	3.5	2.1	0.5	0.5
6	29	0.66	+	MR	+	2.4	2.2	4.0	2.5	0.6	0.6
	124	1.3	+	MR	+	3.2	5.1	5.9	3.9	0.9	0.6
	138	1.4	+	0	PMV	3.7	2.9	4.6	2.7	0.9	0.8
7	29	0.64	0	0	+	1.6	1.5	3.0	2.0	0.5	0.5
	88	1.05	+	0	+	2.5	2.2	4.2	2.5	0.6	0.6
8	36	0.69	+	0	+	2.4	2.1	3.1	2.2	0.4	0.4
9	38	0.63	0	MR	+	1.9	2.1	3.2	2.0	0.5	0.4
	65	0.74	+	MR	+	2.5	2.2	4.4	2.2	0.7	0.7
10	17	0.48	0	0	0	1.6	1.5	2.6	1.7	0.5	0.5
					Males						
11	0.07	0.23	0	0	0	1.3	1.3	2.4	1.7	0.4	0.4
	40	0.75	+	0	+	2.4	1.7	3.9	2.7	0.6	0.5
12	12	0.46	0	0	0	1.4	1.3	2.7	1.6	0.3	0.3
	37	0.65	+	0	+	2.0	1.8	3.4	2.2	0.6	0.6
13	13	0.52	0	0	+	2.0	1.5	2.8	1.6	0.4	0.4
	45	0.74	0	0	+	2.6	2.2	3.8	2.1	0.4	0.5
14	24	0.58	0	0	0	1.7	1.7	3.2	1.7	0.6	0.6
	56	0.79	+	0	+	2.3	1.6	3.4	2.0	. . .	. . .
15	24	0.64	+	0	+	2.5	2.3	4.1	2.4	0.6	0.6
	69	1.1	+	0	+	2.8	2.6	4.7	3.0	0.8	0.8

* Deceased, age 11 months after mitral valve replacement.
AR = aortic regurgitation; ARD = aortic root dimension; BSA = body surface area; LAD = left atrial dimension; LVDD = left ventricular diastolic dimension; LVSD = left ventricular systolic dimension; MR = mitral regurgitation; MVP = mitral valve prolapse; PMV = prosthetic mitral valve; PWT = left ventricular posterior wall thickness; VST = ventricular septal thickness; 0 = absent; + = present.

veal features of the Marfan syndrome, except for isolated MVP in 1 mother. Each child underwent detailed ophthalmologic examination. Cardiac auscultation was performed with the patient in the supine, left lateral decubitus, and upright positions. Skeletal, ocular, and family history data are summarized in Table I. Thirteen of the 15 patients were followed up for 8 to 109 months (mean 45). Two patients were lost to follow-up. No patient was taking medication when first evaluated; 2 were subsequently treated with digoxin for atrial flutter and 1 with propranolol as prophylaxis against aortic dilatation and dissection.[4,16]

Echocardiograms were performed with the patient supine using a Smith-Kline Ekoline 20A instrument with a Honeywell 1956 recorder and a 3.5 or 2.25-MHz Aerotech transducer. The transducer position was adjusted along the lower left sternal border to record the left ventricular cavity, with simultaneous visualization of the posterior wall and ventricular septum just below the mitral valve tips. Damping was adjusted to obtain clear endocardial and epicardial echoes. Aortic root and left atrial recordings were made at the level of the aortic valve leaflets. Left ventricular diastolic dimension, left ventricular systolic dimension, ventricular septal thickness, posterior wall thickness, aortic root dimension, and left atrial dimension were measured as described by Sahn et al.[17] Mitral valve prolapse was defined as deflection of a mitral leaflet posterior to the "C" point by at least 2 mm throughout systole or beginning in midsystole. Each measurement was plotted as a linear function of body surface area, with normal values defined as those falling within the 95% prediction intervals for normal children described by Henry et al.[18]

Results

The clinical cardiovascular features at the first, preoperative (where pertinent), and latest evaluations at our institution are summarized in Table II. On the first physical examination, 2 patients had an isolated, apical, nonejection systolic click, 5 had a pansystolic apical murmur consistent with mitral regurgitation (MR), and 5 had normal findings on auscultation. None had audible aortic regurgitation (AR) or clinical evidence of any congenital heart defect.

The most recent or immediate preoperative physical examination of the 13 children available for follow-up examination revealed an isolated, apical, nonejection systolic click in 6, isolated MR in 4, and MR and AR in 1. Seven patients had progression of mitral valve dysfunction, defined as appearance of a new systolic click, an increase in the murmur of MR by at least 2 grades, or appearance of congestive heart failure in the absence of AR. Four patients developed severe MR and underwent valve replacement. One of these patients died immediately after mitral valve surgery at age 11 months of left ventricular dysfunction and the other (Patient 2) had AR during follow-up.

Echocardiographic measurements standardized for body surface area were compared with each other and with data from Henry et al[18] for normal children. The most frequent abnormality at the first examination, present in 9 patients, was aortic root enlargement, which was >95% prediction intervals for normal children. Nine patients, 5 of whom had neither a systolic click nor an apical systolic murmur on auscultation, had MVP. The only other abnormality was an increased left ventricular diastolic dimension in 4 patients, 3 of whom had MR.

The echocardiograms taken from each of the 13 patients during their follow-up study were examined. All patients had an aortic root dimension at or above the normal range; the increase in aortic root diameter was greater than predicted on the basis of growth in body surface area in most cases (Fig. 1). All patients had or developed MVP. Nine had echocardiographic criteria for progression of mitral valve dysfunction, specifically, appearance of new MVP or development of left atrial or left ventricular enlargement in the absence of AR. Four patients with increased left ventricular diastolic dimensions required mitral valve replacement (Fig. 2). For most examinations, left atrial and ventricular systolic dimensions were within normal limits, and in all the echograms ventricular septal and posterior wall thicknesses were normal.

Discussion

Review of cardiac involvement in children with the Marfan syndrome: Reports of infants and young children with the Marfan syndrome have focused on severely affected patients who usually had prominent cardiovascular involvement and most were published before the availability of echocardiography.[19–29] Many patients <3 years of age had MR, but not AR; nonetheless, dilated sinuses of Valsalva were documented often on angiocardiography or at autopsy. In the largest pediatric series, 36 patients <16 years old, including 2 infants, were described; most had apical nonejection systolic clicks, MR alone or with a click, or AR as well as dilatation of the sinuses of Valsalva detected at cardiac catheterization.[27]

There are few reports of the cardiac manifestations of the Marfan syndrome in young children that include echocardiography. Brown et al[14] studied 35 patients, 14 of whom were <16 years but none <3 years. Spangler et al[13] reported on 26 patients, including 6 <16 years and 3 infants. Two infants had both AR and MR and 1 had MR and congestive heart failure; all had MVP, left atrial enlargement and aortic dilatation on echocardiography. These studies, and several studies of echocardiograms in adult patients with Marfan syndrome,[30] suggest the following: First, aortic dilatation may appear early in life. Second, aortic dilatation precedes the appearance of AR in some instances. Third, aortic dilatation may not be detectable by clinical examination or chest radiography. Finally, MVP is common and may be associated with severe MR. These cross-sectional studies, however, have provided little insight into the natural history of aortic dilatation and mitral valve dysfunction in the Marfan syndrome.

The group of patients described in this study is likely to be more representative of young patients with Marfan syndrome than any heretofore published because it is not composed solely of severely affected patients referred for management of cardiovascular, ocular or skeletal problems, but also of patients ascertained through family studies. All 7 children with a family history of the Marfan syndrome were first evaluated because of parent or physician concern about whether the child was affected and not because of a specific medical complaint.

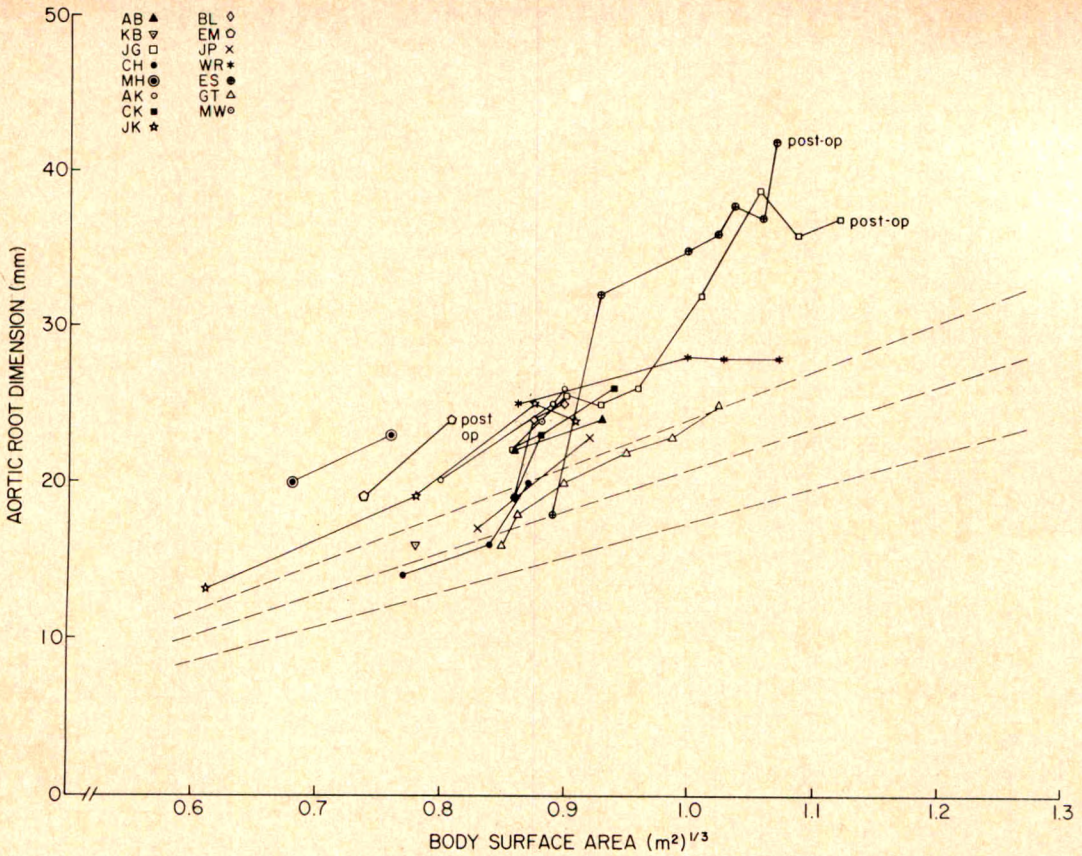

FIGURE 1. Aortic root diameter in the Marfan syndrome. M-mode echocardiographic aortic root dimension is plotted versus the cube root of body surface area. Three patients who had postoperative (post-op) echocardiography after mitral valve replacement are indicated. Patient 1 (MH) died shortly after mitral valve surgery and did not undergo postoperative echocardiography. The **dashed lines** indicate the mean values and 95% prediction intervals for aortic root dimension in normal children.

Sporadic cases of the Marfan syndrome tend to be more severely affected, on an average, than familial cases[1,2] and account for about one third of patients of all ages with Marfan syndrome. Eight of 15 of our patients did not have an affected parent, but were referred for management of specific problems, 4 for heart murmurs. The fact that more than half of our patients were sporadic suggests a possible sampling bias. This disparity may be related to the young age of our population and expression of the more afflictive phenotype at an earlier age. Sporadic and familial cases were first evaluated at the same mean age (19 months) when only sporadic cases had MR (5 versus 0), whereas aortic root dilatation and MVP on echocardiographic examination were similar in both groups (4 versus 3) and (5 versus 4). All 4 patients who required mitral valve replacement were sporadic. Whether clinical differences in sporadic versus family history cases reflect genetic heterogeneity will be answered when basic defects or their molecular markers are discovered.[31]

Aortic dilatation: In this study, almost all patients had aortic root dilatation. Only 1 patient had AR detected with auscultation. This patient also had the largest aortic root diameter (3.5 cm/m^2) when the murmur was first heard, in keeping with preliminary evidence that AR results from progressive stretching of the upper cusp attachments around the sinotubular ridge.[32]

To assess changes in aortic root dimension with increasing body surface area, measurements from all echocardiograms were plotted (Fig. 1). For 6 patients, the slope of the line was normal, although the aortic root diameters were all >95% prediction intervals for normal children. Seven patients showed periods during which the slope of the line was increased, a finding not likely to be due to growth. The regression equation with 95% prediction intervals, derived from the data of Henry et al,[18] for normal children that predict aortic root diameter from body surface area is 26.8 [BSA$^{1/3}$] − 6.1 ± 16%. Overall, for our study group at latest follow-up, the regression equation is 68.0 [BSA$^{1/3}$] − 38.6, indicating both a greater aortic root dimension and a greater slope.

Aortic root dilatation is the most common cardiovascular abnormality in adult patients with Marfan syndrome.[2,13,14] This study shows that aortic root dilatation is already manifest in early childhood in most patients. There are isolated studies of patients with gross dilatation of the sinuses of Valsalva and histopathologic characteristics of medial degeneration present in utero.[1,33] Thus, aortic root dimension is an objective criterion of the Marfan syndrome, even in

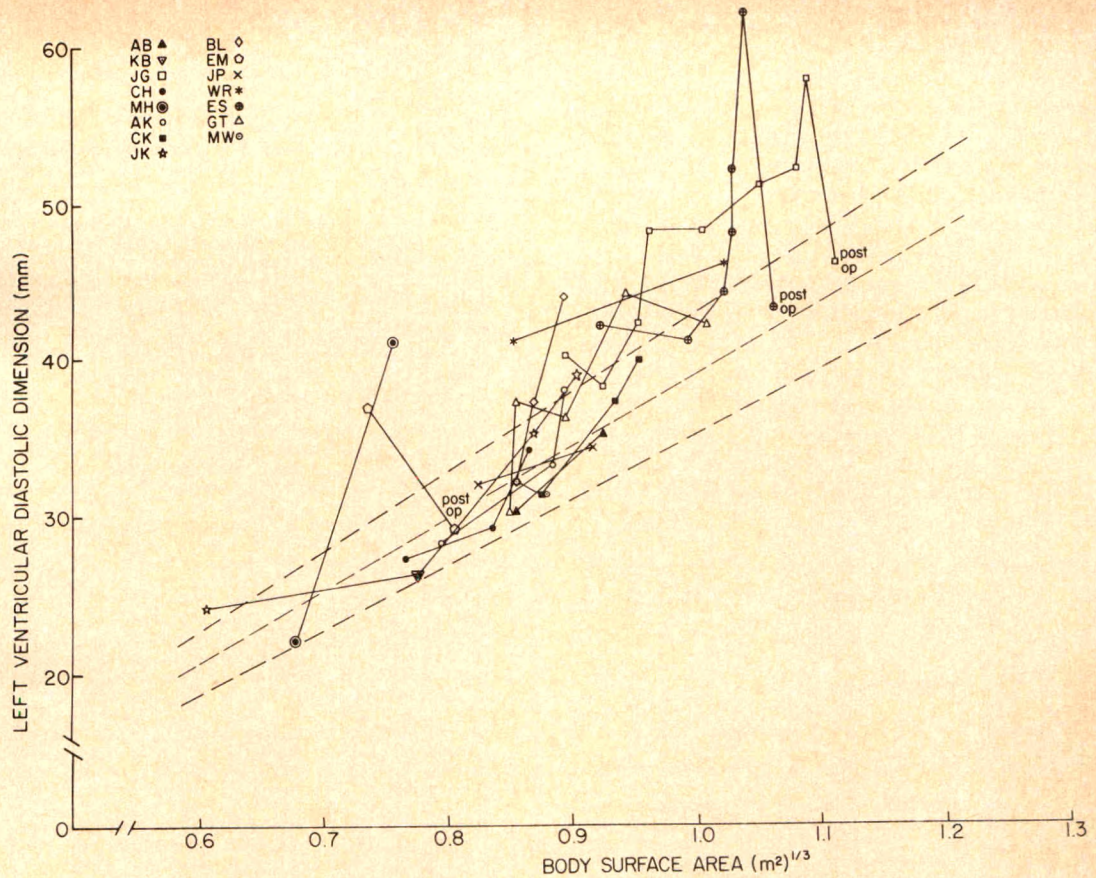

FIGURE 2. Left ventricular end-diastolic dimension in the Marfan syndrome. M-mode echocardiographic left ventricular end-diastolic dimension is plotted versus the cube root of body surface area. Three patients who had postoperative echocardiography after mitral valve replacement are indicated. Patient 1 (MH) died shortly after mitral valve surgery and did not undergo postoperative echocardiography. The **dashed lines** indicate the mean values and 95% prediction intervals for left ventricular end-diastolic dimension in normal children.

infancy. Moreover, the aortic root progressively enlarges in the pathologic range throughout childhood, a process which, when accelerated, may lead to AR before adolescence.

No child in this study required aortic surgery. Our criteria for performing elective, prophylactic repair of the ascending aorta with a composite graft are moderate AR and sinus of Valsalva dilatation of about 5.5 cm.[34] Periodic clinical and echocardiographic evaluation of all patients of any age with Marfan syndrome is mandatory to establish the optimal time for surgical intervention. For the child without AR, an annual echocardiogram is recommended.

Mitral valve dysfunction: Involvement of the mitral valve is almost as common as aortic root dilatation in the Marfan syndrome and may be severe enough to represent the major cardiovascular morbidity, particularly in children.[6,20,23,25,27–29,35,36] In a longitudinal review of 120 patients <22 years, mitral valve dysfunction in the Marfan syndrome presented as MVP and, as opposed to idiopathic MVP, progressed clinically in about half.[37]

Within the group reported here, 5 children progressed from having no to definite auscultatory or echocardiographic evidence of MVP. Five girls had MR when first evaluated (mean age 18 months); 4 developed more severe valvular dysfunction, congestive heart failure, and progressive left ventricular dilatation. All had successful mitral valve replacement (mean age 78 months). One died soon after operation at age 11 months and, in retrospect, surgery might have been indicated earlier because of severe failure to thrive. A marked reduction in left ventricular diastolic dimension followed valve replacement in all 3 survivors. Although the 4 patients who had severe mitral valve dysfunction were female, males have MVP and MR nearly as frequently as females.[37] We cannot be certain from our series or from the literature whether the early and severe MR in some females reflects true sex influence on phenotypic expression, variability due to genetic heterogeneity or sampling bias. Idiopathic MVP is expressed more frequently, if not more severely or earlier, in females.[38,39]

Mitral valve replacement in young children is usually accompanied by 3 considerations for the long term. First, because the homograft valve tends to calcify or otherwise degenerate and because of the substantial life expectancy of the young patient with Marfan syndrome, we have routinely implanted the St. Jude Medical prosthesis. Second is the need for long-term anticoag-

ulation. Third is the potential development of valve-patient mismatch as the child grows, which should not be a problem in the Marfan syndrome because the anulus undergoes substantial dilatation and will accept prosthetic valves of diameter sufficient for hemodynamic function in adulthood. Another consideration unique to the Marfan syndrome is best illustrated by Patient 2 in this series. Regardless of mitral valve dysfunction, the aortic root will likely progressively dilate and lead to a need for composite repair. When mitral dysfunction is early and severe, the patient will require 2 separate procedures. However, for selected patients it may be possible to delay mitral repair until the patient is also a candidate for aortic surgery and to perform a combined procedure. On the other hand, it is probably unwise to delay aortic repair in anticipation of progressive mitral valve dysfunction because of the risk of aortic catastrophe once the root is markedly dilated.

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Physical Conditioning and Left Ventricular Performance in the Elderly: Assessment by Radionuclide Angiocardiography

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In contrast to young persons, normal elderly persons who undergo symptom-limited dynamic exercise demonstrate a decrease in left ventricular (LV) contractile performance characterized by a decrease in LV ejection fraction. To test the hypothesis that physical conditioning can be achieved in older persons and produces improvement in the exercise-induced decrease in LV ejection fraction observed during normal aging, we examined 24 normal elderly persons (mean age 72.0 years) before and after a 12-week program of physical training. The subjects had been screened for evidence of cardiovascular disease including rest and exercise stress electrocardiograms. All subjects underwent rest and exercise upright sitting radionuclide angiocardiography before and after the training program.

The subjects achieved cardiovascular training effects as measured by increased functional capacity and decreased double product at one-half the maximum work load attained at the initial stress test. A significant increase occurred after training in the cardiac index response to exercise ($p < 0.02$) and in the augmentation of the end-diastolic volume index produced by exercise ($p < 0.05$). However, the exercise-induced decrease in LV ejection fraction and increase in LV end-systolic volume index remained unaltered by training.

In conclusion, although older persons can achieve overall training effects from a program of physical conditioning, the age-associated differences in LV contractile performance remained unchanged. Our data suggest that deconditioning is not a significant contributor to the decline in LV contractile performance in the elderly.

A decline in cardiovascular performance is a general phenomenon of the aging process, including decreased cardiac output and heart rate.[1,2] In response to dynamic exercise, significant reductions in maximal oxygen consumption, heart rate, and cardiac output have been well documented.[3,4] In addition, a recent study from our laboratory used radionuclide angiocardiography (RNA) to demonstrate a diminution in left ventricular (LV) ejection fraction in response to exercise in a group of untrained elderly persons free of overt cardiovascular disease.[5] Possible mechanisms for age-associated changes in cardiovascular function are numerous and include decreased intrinsic contractility, altered preload or afterload, altered sympathetic responsiveness, chronic deconditioning, and clinically unrecognized cardiac disease.

Physical conditioning is a long-recognized method of improving cardiovascular performance. Its beneficial effects are well documented in the young.[6] Features of the cardiovascular response to conditioning include increased oxygen extraction and systemic arteriovenous oxygen difference which, along with enhanced stroke volume and maximum cardiac output, result in augmented maximal oxygen consumption. Some clinical observations supporting these changes consist of diminished heart rate at rest, increased functional capacity, and rapid return to resting hemodynamic status after acute exercise. Radionuclide ventriculography demonstrates augmented cardiac output and increased end-diastolic volume in response to exercise in young athletes after high-intensity physical conditioning.[7] In middle-aged patients with coronary artery disease, physical conditioning increases functional capacity, although its specific effects on ventricular function are less uniformly recognized.[8–10] Some studies[11,12] support

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the view that older persons cannot achieve training effects by physical conditioning. However, others[13–15] suggest that the elderly can indeed achieve a state of physical conditioning.

Methods

Subjects: Forty-two subjects aged ≥65 years were recruited primarily from 3 sources: a volunteer pool from the Duke University Center for the Study of Aging and Human Development, residents of the North Carolina Methodist Retirement Home, and participants in the Duke Institute for Learning in Retirement. All potential subjects underwent initial evaluation including medical history, physical examination, and electrocardiography at rest and during upright sitting bicycle ergometry as will be described. Criteria for exclusion from the exercise program consisted of historical or physical evidence of cardiovascular disease, active disease known to affect the cardiovascular system, medications known to influence cardiovascular function, and electrocardiographic changes interpreted as indicative of ischemic heart disease at rest or during exercise. Fifteen subjects were excluded from participation on the basis of these criteria. The ages, clinical status, and previous activity levels of subjects from all sources were similar. Consequently, the results reflect pooled data from all 3 sources.

Radionuclide angiocardiography: First-pass radionuclide angiocardiograms were obtained using a multicrystal gamma camera (System Seventy-Seven, Baird-Atomic, Inc.) fitted with a 2.54-cm parallel-hole collimator.[16] Each study was performed by the rapid bolus injection of a small volume containing 10 mCi of technetium-99m pertechnetate into an indwelling catheter placed in an external jugular or antecubital vein. Data were acquired at a framing rate of 25 ms for a total of 1 minute for each study. All subjects were studied in the upright sitting position from an anterior projection.

Computer processing of the data collected from each study used the Baird-Atomic System Seventy-Seven clinical software package. Briefly, a curve of count changes in the left ventricle was used to determine end-systolic times of individual beats. Data from 3 to 6 beats were superimposed to form a background-corrected representative cardiac cycle. A 21% isocount line delineated the end-diastolic and end-systolic measurements of the left ventricle. Volume determinations applied the area-length method of Sandler and Dodge[17] to end-diastolic and end-systolic edge contours. Those contours were determined with a sonic digitizing device coupled to a PDP-11/45 computer. Regional wall motion was analyzed by a review of videotape display of 21% isocount contours of sequential cardiac cycles. Regional function was also analyzed by calculating ejection fraction for each crystal conforming to the left ventricle image. The ejection fraction was displayed on a 16-color-coded scale, each color denoting a 6.25% difference in ejection fraction.

Exercise testing protocol: Rest and exercise studies were carried out on an upright isokinetic bicycle ergometer (Fitron, Lumex). The electrocardiogram (routine limb leads and V_5 and V_6) was monitored for rate, rhythm, and S-T segment changes at rest throughout the period of exercise and until the heart rate had returned to the preexercise baseline level. Blood pressure was monitored by a cuff sphygmomanometer throughout the testing and post-testing period. After a radionuclide angiocardiogram at rest, each subject was then instructed to pedal against work loads beginning with 100 kpm/min (980 J) and incrementally augmented thereafter until exhaustion. Exercise radionuclide angiocardiography was performed at the maximal symptom-limited work load achieved. Exercise testing was repeated at the conclusion of the physical conditioning program with a slight modification. The resting study was performed as just described, whereas the exercise radionuclide angiocardiography was acquired at the same level of work load as the maximum achieved in the pretraining study.

Physical conditioning program: The subjects participated as a group in 3 exercise sessions per week for 12 consecutive weeks. Each period consisted of several minutes of stretching exercise and warmup on bicycle ergometers at no work load. The aerobic portion of the session consisted of 25 to 30 minutes of continuous pedaling at a fixed rate against predetermined tension, so that each participant's heart rate would be maintained within a training range (70 to 85% of heart rate achieved at the time of initial bicycle ergometer testing). Radial pulse was monitored during each training session and work loads were adjusted on a weekly basis to maintain the heart rate in the training range. Each training session concluded with a brief period of "cool down" bicycling without tension. All sessions were supervised by at least 2 observers trained in acute cardiac care.

Statistical analysis: The data were largely examined by analysis of variance. Because men and women may have responded differently to the training program, gender (male and female) was considered a between-subject factor. Similarly, because older subjects may have shown a different pattern of response compared with younger subjects, age (≤70 years old and >70 years old) was also considered a between-subject factor. Time (before and after training) served as a within-subject factor, so that main effects for time indicated significant changes before and after training. State (at rest and during peak exercise) also served as a within-subject factor for variables in which change from rest to exercise was considered to be important. Chi-square analyses were used to analyze a selected matrix of segmental wall motion abnormalities.

Results

Of 27 subjects initially enrolled in the exercise program, 24 (18 women, 6 men; mean age 72.0 ± 6.2 years) completed the study. Two participants had dropped out for medically unrelated reasons, and 1 was not included because of medication use unknown to the investigators until after enrollment. Attendance at the exercise training sessions was excellent, with all subjects participating in at least 90% of the scheduled sessions. No injuries or morbid cardiac events occurred during the entire study.

Physical conditioning: Physical conditioning was assessed by work load on the bicycle ergometer and rate-pressure product at a matched submaximal work load. Both of these variables improved when initial and final bicycle ergometer results were compared. Work load on the bicycle increased from 690 ± 151 kpm/min to 758 ± 141 kpm/min ($p < 0.008$), and rate-pressure product at matched submaximal work load decreased from 14,300 ± 3,070 to 13,400 ± 2,230 ($p < 0.02$). Other physiologic variables of cardiovascular performance measured before and after training are depicted in Table I. Analysis of variance disclosed no significant interactions attributable to sex difference or age stratification, suggesting that both male and female subjects changed in the same way whether in the younger or older segment of our subject group. Consequently, all analyses were collapsed over age and sex.

Radionuclide assessment of global LV performance: Each measure of cardiac function (LV ejection fraction, cardiac output, cardiac index, end-systolic

volume index, and end-diastolic volume index) was considered in a separate 2 by 2 analysis of variance. Table II presents the means and standard deviations for each variable at rest and at peak exercise before and after the 12-week conditioning program. Analysis of variance for cardiac output revealed a significant main effect for State ($F(1,20) = 131$, $p < 0.001$), with cardiac output increasing from rest to exercise. This increase in cardiac output in response to exercise was comparable before and after training, as evidenced by the absence of a State × Time interaction. However, analysis of variance for cardiac index revealed not only significant main effects for Time ($F(1,20) = 4.94$, $p < 0.03$) and State ($F(1,30) = 296$, $p < 0.0001$) but also a significant State × Time interaction ($F(1,20) = 5.22$, $p < 0.03$). Analysis of simple effects revealed that although resting cardiac index remained constant before and after training, the cardiac index during exercise increased from 5.89 ± 0.97 liters/min/m^2 to 6.71 ± 1.71 liters/min/m^2 after training ($F(1,20) = 6.19$, $p < 0.02$), accounting for the significant interaction.

End-systolic volume index did not change over Time, although there was a significant State main effect ($F(1,20) = 22.3$, $p < 0.0001$); that is, there was a significant increase in end-systolic volume index from rest to exercise. In the absence of a significant interaction, it was apparent that this increase in systolic volume index was unchanged before and after training. However, consideration of end-diastolic volume index revealed a significant main effect for State ($F(1,20) = 34.2$, $p < 0.0001$) and a significant Time × State interaction ($F(1,20) = 6.25$, $p < 0.02$). Examination of simple effects revealed that although the resting end-diastolic volume index did not change from before to after training (59.4 ± 8.5 ml/m^2 to 57.9 ± 13.0 ml/m^2, difference not significant), the end-diastolic volume index did increase significantly during exercise, from 67.9 ± 14.4 ml/m^2 to 76.6 ± 20.2 ml/m^2 ($F(1,20) = 4.26$, $p < 0.05$) after the conditioning program.

LV ejection fraction demonstrated main effects for both Time $F(1,20) = 6.55$, $p < 0.03$) and State ($F(1,20) = 10.65$, $p < 0.003$). However, no significant interaction was seen between Time and State. In other words, the decrease in LV ejection fraction of these elderly subjects in response to exercise persisted unaltered despite physical conditioning.

Radionuclide assessment of regional wall motion: Regional wall motion abnormalities were not commonly seen in the resting studies. Twenty-one subjects demonstrated no wall motion defect at rest before or after training. As shown in Table IIIA, a single subject had a wall motion abnormality at rest before and after the

TABLE I Effect of Physical Conditioning on Overall Cardiovascular Function in the Elderly

Variable	Before Training (mean ± SD, n = 24)	After Training (mean ± SD, n = 24)
Resting heart rate (beats/min)	70 ± 13	72 ± 13
Resting systolic BP (mm Hg)	134 ± 18	138 ± 18
Resting diastolic BP (mm Hg)	74 ± 10	77 ± 12
Maximum time achieved on bicycle ergometer (min)	7.71 ± 1.47	8.45 ± 1.75*
Maximum work load achieved on bicycle ergometer (kpm/min)	690 ± 151	758 ± 141†
Heart rate × blood pressure product matched to half maximal work load achieved before training	14,300 ± 3,070	13,400 ± 2,230‡
Maximum exercise heart rate (beats/min)	146 ± 17	140 ± 17
Maximum exercise systolic BP (mm/Hg)	188 ± 22	182 ± 22
Maximum exercise diastolic BP (mm/Hg)	78 ± 17	74 ± 16

* $p < 0.007$.
† $p < 0.008$.
‡ $p < 0.02$.
BP = blood pressure; kpm = kilopond meter; SD = standard deviation.

TABLE II Effects of Physical Conditioning on Global Left Ventricular Performance Assessed by Radionuclide Angiocardiography

Variable	Before Training (mean ± SD)	After Training (mean ± SD)*
Rest studies		
Cardiac output (liters/min)	4.86 ± 0.97	5.03 ± 1.24
Cardiac index (liters/min/m^2)	2.78 ± 0.67	2.84 ± 0.71
End-diastolic volume index (ml/m^2)	59.4 ± 8.5	57.9 ± 13.0
End-systolic volume index (ml/m^2)	19.8 ± 6.1	17.5 ± 7.9
Left ventricular ejection fraction (%)	67.1 ± 9.0	71.0 ± 10.6
Exercise studies†		
Cardiac output (liters/min)	9.94 ± 2.97	11.4 ± 4.0
Cardiac index (liters/min/m^2)	5.89 ± 0.97	6.71 ± 1.71
End-diastolic volume index (ml/m^2)	67.9 ± 14.4	76.6 ± 20.2
End-systolic volume index (ml/m^2)	27.2 ± 11.6	28.6 ± 13.3
Left ventricular ejection fraction (%)	61.5 ± 10.6	64.0 ± 10.2

* Analysis of variance probabilities described in Results section.
† Exercise studies performed at work loads as described in Methods section.
SD = standard deviation.

TABLE III Effect of Physical Conditioning on Ventricular Wall Motion Assessed by Radionuclide Angiocardiography

After Training \ Before Training	Patients With Normal Wall Motion	Patients With Abnormal Wall Motion
A. At Rest		
Normal	21	1
Abnormal	1	1
B. With Exercise		
Normal	10	7
Abnormal	2	3

TABLE IV Effect of Prior Exercise Wall Motion Abnormalities on the Left Ventricular Ejection Fraction Exercise Response After Conditioning*

	Mean Δ LVEF ($LVEF_{EX}$–$LVEF_{REST}$) (%)	
	Before	After
Group A	−2.1 ± 9.4	−6.2 ± 9.7†
Group B	−8.4 ± 9.4	−7.4 ± 10.3†

* Exercise studies performed at work loads as described in Methods section.
Group A: No exercise segmental wall motion abnormality before training (n = 13).
Group B: Exercise segmental wall motion abnormality present before training (n = 11).
† p = not significant.
LVEF = left ventricular ejection fraction.

training program, and 1 subject each developed or apparently resolved a resting wall motion defect during the course of the training protocol. No alterations in clinical status or electrocardiograms accompanied the changes in radionuclide results.

Table IIIB depicts the training effects on regional wall motion in response to exercise. Two subjects had studies technically inadequate for wall motion analysis. As in the resting studies, participants tended to have normal wall motion with exercise before and after training or abnormal wall motion, uninfluenced by training. However, 7 subjects with pretraining focal wall motion abnormalities had no defects when exercised to the same work load after training. Two subjects demonstrated previously undetected abnormal wall motion after training. The chi-square value for this analysis was not significant ($p > 0.40$). However, the small number of subjects in each cell may preclude meaningful statistical interpretation of these results.

We further examined the effect of conditioning on the LV ejection fraction response of subjects who had shown exercise segmental wall motion abnormalities before training. The subjects were divided into 2 groups based on the absence (Group A, n = 13) or presence (Group B, n = 11) of wall motion abnormalities with exercise before training. However, no significant difference appeared between the groups' LV ejection fraction responses to exercise before or after conditioning (Table IV).

Discussion

Our study confirms and extends earlier published work from this laboratory that documented the decrease in LV contractile performance in response to exercise seen in healthy aging subjects.[5] In addition to a decrease in LV ejection fraction with exercise, we showed that decreases in end-systolic volume observed in the young during exercise[7] do not occur in the elderly. The current study demonstrates that although elderly persons can achieve physical conditioning effects, the decline in LV performance in response to exercise persists.

Comparison of physical conditioning response in the elderly to other subject populations: The results of the present investigation prompt comparison to previous studies in 2 other groups, young healthy persons and patients with coronary artery disease. After training, young conditioned male athletes demonstrated decreased resting heart rate and LV ejection fraction, whereas resting end-systolic and end-diastolic volume increased with the net result being an unaltered resting cardiac output.[7]

In contrast, the present study shows that resting heart rate, cardiac index, and volume indexes remained unchanged in the elderly, whereas resting LV ejection fraction increased. The present findings are consistent with the response reported by Verani et al[10] for training effects in patients with documented coronary artery disease. The failure of rest end-diastolic volume to increase with training in the elderly may be a reflection of diminished diastolic compliance of the older ventricle in the resting state.

With regard to the exercise response after training, the elderly demonstrated unchanged heart rate and LV ejection fraction, while cardiac output increased because of minor augmentation in both end-diastolic and stroke volume. This observation at a work load matched to the pretraining maximal work load resembles the response of the young to post-training maximal work load. In our elderly subjects, the exercise-induced decline in LV ejection fraction and the concomitant failure to decrease end-systolic volume resembled the response noted in patients with coronary artery disease.[16] The overall change in LV ejection fraction from the resting state to exercise was unaffected by conditioning in the elderly, analogous to findings in patients with coronary artery disease.[9] By way of speculation, adaptation of the aging ventricle may confer minimal ability to dilate in response to stress but without concomitant ability to increase contractile performance.

As might have been expected, resting wall motion abnormalities were rarely seen in our subjects either before or after training, distinct from patients with coronary disease. Furthermore, patients with coronary artery disease have improvement in resting wall motion with training.[10] After conditioning, most of the subjects' wall motion in response to exercise remained unchanged (n = 13) or improved (n = 7), whereas 2 subjects displayed previously undetected wall motion abnormalities, an overall finding similar to those of Verani et al.[10] A cautionary note seems warranted in this discussion.

Reasonable care must be used in interpreting all minor changes in the radionuclide angiocardiographic studies of the elderly after training, because apparent statistical significance may not confer physiologic or clinical relevance.

Possible causes of the age-related decline in cardiac performance: Several factors, both methodologic and biologic, may explain our inability to induce improvement in ventricular performance in this elderly population after training. With respect to the present method, an easily conducted protocol was felt necessary to discourage dropouts in these elderly subjects. However, in contrast to results in younger individuals, 12 weeks of training may not be a enough to achieve optimal conditioning effects in the elderly. The current study is unique in testing elderly persons with upright sitting ventriculography at rest and with exercise using stress identical to that used in their physical conditioning program. A previous report from this institution documented the reproducibility of upright sitting radionuclide ventriculography at rest and with upright bicycle ergometry exercise.[18]

LV ejection fraction is one index of LV contractile performance. The determinants of LV contractile performance include preload, afterload, and contractile state. Biologic factors that might influence these determinants to prevent significant conditioning-induced modification of LV performance in response to exercise include: (1) inability of the heart to respond to the repetitive sympathetic stimulation associated with cardiovascular training, (2) decreased response to augmented preload by the Frank-Starling mechanism, (3) inability to respond to exercise-induced increase in afterload, (4) decreased overall contractility rendering specific myocardial training unattainable, (5) inability to improve myocardial oxygen extraction, (6) occult coronary artery disease, and (7) a state of chronic deconditioning in the elderly that is less readily reversed than in younger persons.

Loss of sympathetic responsiveness to catecholamines occurs during aging.[19] This change has been attributed to mechanisms both dependent[20] and independent[21] of alterations in adrenergic receptors. A failure of the Frank-Starling mechanism could account for inability of the older ventricle to respond to stress in a manner similar to that of the young ventricle. However, the minimal increase in stroke volume produced by augmented end-diastolic volume with exercise achieved by training in the elderly suggests a response similar to the training effect observed in young athletes. As such, current observations on changes in end-diastolic volume from rest to exercise in the pre- and post-training period do not support a significant decrement in the Frank-Starling mechanisms. Despite the failure of exercise to induce a decline in end-systolic volume in this study, afterload (as reflected in the blood pressure response) does not demonstrate changes with exercise after training in our subjects. Using an animal model, Yin et al[22] described increased aortic impedance in response to exercise in old dogs. In addition, in vitro preparations of senescent rat hearts display decreased compliance and augmented stiffness characteristics.[23] These 2 studies may have implications for the description of cardiac performance in aging man. The investigation reported herein does not address decreased myocardial oxygen extraction as a potential cause of the decrease in LV contractile performance. Hartley et al[24] suggested that inability to increase the systemic arteriovenous oxygen difference may indeed be an important factor in the failure to achieve more significant cardiovascular training in the elderly. The present study cannot exclude this possibility.

Occult cardiovascular disease may explain a diminished overall training effect or the ability to influence global or regional LV performance. Probability alone predicts a significant prevalence of coronary artery disease in this age group. However, all the subjects were asymptomatic, without significant physical findings, and each failed to demonstrate evidence of ischemic heart disease on electrocardiograms at rest or during stationary bicycle exercise. These findings decrease somewhat the likelihood of encountering occult coronary disease in this population.

Coronary artery disease per se should not prevent the attainment of a training effect. Studies have demonstrated the ability to achieve physical conditioning in patients with documented coronary artery disease.[8,25] Despite the overall physical conditioning attained in those patients with coronary artery disease, few studies have shown meaningful improvement in either global or regional LV performance by physical conditioning in patients with coronary artery disease.[9,10] The present study suggests that the postconditioning changes in overall cardiovascular performance and LV contractile performance of asymptomatic clinically disease-free elderly persons minimally resembles the training responses seen in both young athletes and middle-aged patients with coronary artery disease. The significance and implications of these possible similarities are not entirely apparent. Additionally, the role of life-long physical conditioning in preventing or retarding the observed decline in LV contractile performance remains untested in man.

Deconditioning per se would not appear to be either the sole or the major determinant of decline in LV contractile response to exercise observed in older man. Further studies directed at noninvasive assessment of ventricular compliance characteristics and overall contractility appear to be one fruitful approach to the perplexing problem of waning cardiovascular performance during senescence.

Acknowledgment: The coordinated efforts of numerous persons were required to complete this study. Unfortunately, because of the lack of space here, many will go individually unrecognized. However, we gratefully acknowledge Drs. Robert Nebes and Donald Neisch for permission to study their patients, Rosemarie Schuler, NMT, and the staff of the Nuclear Cardiology Laboratory, Duke University Medical Center, for their cheerful and competent technical skills, Dr. Frederick R. Cobb for his thoughtful criticism, F. Paul Koisch, without whose help the training sessions could not have been conducted, Paula Crockett, RN, for assisting in supervising the exercise sessions, Terri Needels, PhD, and Leslie C. O'Toole for their assistance in computer programming and data

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Abnormal Thallium-201 Scans in Patients With Chest Pain and Angiographically Normal Coronary Arteries

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We reviewed the exercise thallium-201 (Tl-201) scans and clinical data of 41 patients with chest pain and normal coronary arteries to identify clinical factors associated with "false-positive" studies. Exercise Tl-201 studies were performed before angiography and often precipitated referral. Sex, beta-blocker therapy, anginal pattern, and results of exercise electrocardiography were evaluated and compared with Tl-201 imaging. A negative Tl-201 study was the most common finding ($p < 0.005$). Of the 41 patients, 11 (27%) had abnormal exercise Tl-201 scans. No clinical factor was significantly associated with a false-positive Tl-201 scans. Of the 11 patients with abnormal scans, 9 had ≥1 cardiac abnormality: right bundle branch block in 2, mitral valve prolapse in 3, paroxysmal atrial fibrillation in 2, abnormal left ventricular diastolic pressure in 3, and left bundle branch block in 1. Thus, (1) when results of exercise Tl-201 imaging are used to refer patients for angiography, "false-positive" Tl-201 studies are common; (2) sex, beta blockade, anginal pattern, and results of exercise electrocardiogram are not useful predictors of a false-positive Tl-201 study; and (3) patients with chest pain, normal coronary arteries, and abnormal Tl-201 scans frequently have other cardiac abnormalities.

The use of thallium-201 (Tl-201) myocardial perfusion imaging in the evaluation of patients with chest pain has significantly increased our ability to detect coronary artery disease (CAD).[1–3] Patients with abnormal Tl-201 scintigrams are frequently referred for coronary angiography. Patients with normal exercise Tl-201 scintigrams have an excellent prognosis in the following 2 years[4] and often are not studied further. We recently noted an increase in the number of patients with abnormal exercise Tl-201 scans and normal coronary arteries. Because the factors that affect the specificity of exercise Tl-201 imaging have not been clarified, we attempted to correlate the results of Tl-201 imaging with exercise electrocardiography and with various clinical characteristics in this group of patients with chest pain and normal coronary arteries.

Methods

Patient population: One hundred fifteen patients with chest pain who underwent coronary angiography also underwent exercise electrocardiography (ECG) and Tl-201 scintigraphy. Patients with valvular heart disease or cardiomyopathy known before angiography were excluded. Forty-one of these patients had no significant (≥50% stenosis) CAD and form the basis of this report.

All 41 patients had exercise Tl-201 and ECG testing ≤4 weeks before catheterization. There were 18 men and 23 women, with a mean age of 53 years (range 27 to 73). No patient had a history or electrocardiographic evidence of myocardial infarction.

Rest and exercise electrocardiography: Rest and exercise electrocardiograms were interpreted by 2 of the investigators without knowledge of the scintigraphic or angiographic results. Q waves ≥0.04 second on the resting electrocardiogram were considered diagnostic of previous myocardial infarction. Patients exercised in the fasting state on a treadmill using the Chung protocol,[5] but medications were not discontinued. Exercise was stopped if the patient achieved the target heart rate or if chest pain or fatigue developed. Leads II, V_3, and V_6 were monitored during exercise and a 12-lead electrocardiogram was recorded immediately before and after exercise. Test results were considered positive, negative, or nondiagnostic according to standard criteria.[5]

Imaging protocol: Patients were injected at peak exercise with 1.5 mCi of Tl-201 followed by a 10-ml saline flush and continued walking for 30 to 60 seconds. Imaging began within 10 minutes of injection in the anterior view, followed by the 40° and 60° left anterior oblique views. Anterior and 40° left anterior oblique views were repeated immediately. If an abnormality was detected on initial images or washout curves (to be described), delayed images were obtained 2.5 to 3 hours after injection. Images were recorded for 10 minutes on a portable gamma camera with a general all-purpose collimator and a 25% window centered on the 80-KeV energy peak. Images were produced on conventional transparency film and

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stored in a computer for image processing and quantitative analysis.

Image analysis: All studies were interpreted jointly during clinical reading sessions by 3 of the investigators who were unaware of the exercise electrocardiogram results. Unprocessed images and quantitative data were used to produce the final interpretation. Quantitative analysis of Tl-201 uptake and washout was performed using the horizontal profile method as described and applied by Berger et al[3] and Watson et al.[6] Decreases in Tl-201 activity thought to be due to breast shadow or valve plane were not read as abnormal. Isolated persistent apical defects were also not read as abnormal because apical thinning may be a normal variation.[7]

Cardiac catheterization: Selective coronary arteriography was performed using the Sones or Judkins technique. Ventriculography was performed in the 30° right anterior oblique projection. Cineangiograms were interpreted independently by 2 observers. Coronary artery stenosis were considered significant when luminal narrowing was ≥50%.

Results

Thallium-201 imaging: Eleven of 41 patients with chest pain but without significant CAD had abnormal Tl-201 images, for a specificity of 73%. Table I summarizes the clinical, electrocardiographic, and scintigraphic findings in the 11 patients with abnormal Tl-201 scintigrams. Seven women and 4 men had false-positive Tl-201 images. Six patients had 2 defects. Two-vessel CAD was suspected in 3 of these patients because defects were in the anatomic distribution of 2 coronary arteries. In the other 3 patients, 2 defects were thought to be caused by a single coronary stenosis because they occurred in the distribution of 1 vessel. Figure 1 is taken from a patient with typical angina and a negative exercise electrocardiogram. Left anterior descending and right CAD were suspected in this patient, who subsequently was found to have normal coronary arteries.

Of the 17 Tl-201 defects found in 11 patients, 12 defects demonstrated partial or complete redistribution and 5 defects were persistent. There were 5 septal defects, 5 inferior defects, 3 posterolateral defects, 3 apical defects, and 1 defect involving the anterolateral segment. All 3 defects involving the apical segments in our series showed redistribution and were associated with other defects, making it more likely that they were abnormal. None of the patients demonstrated abnormal lung uptake of Tl-201.

Of the 74 patients with CAD who underwent exercise Tl-201 imaging, abnormal uptake or washout, or both, was detected in 61, for a sensitivity of 82%, which is within the range reported in other studies.[1–3]

Resting electrocardiogram: Nineteen patients had abnormalities on the resting electrocardiogram. No patient had evidence of myocardial infarction. Two patients had right bundle branch block and 1 patient left bundle branch block. Three patients had ischemic T-wave inversions. Eleven patients had nonspecific T-wave abnormalities. Two patients had left axis deviation (≥ −15°). Twenty-two had normal electrocardiograms. Of the 11 patients with abnormal exercise Tl-201 studies, 6 had normal electrocardiograms, 2 had right bundle branch block, 1 had left bundle branch block, and 2 had nonspecific T-wave abnormalities. Figure 2 is an electrocardiogram from the patient with left bundle branch block. The Tl-201 scan shows a persistent septal defect.

Exercise electrocardiography: Eleven patients had false-positive exercise electrocardiograms, 17 patients had negative tests, and 13 tests were nondiagnostic. Thus, the specificity of the exercise electrocardiogram in this study was 73% and not significantly different from that of Tl-201 imaging. Of the 11 patients with abnormal Tl-201 images, 3 had positive exercise electrocardiograms, 5 had negative electrocardiograms and 3 were nondiagnostic.

Clinical characteristics: *Chest pain:* Eighteen patients had typical effort angina and 23 had atypical chest pain. Thirteen patients with typical angina and

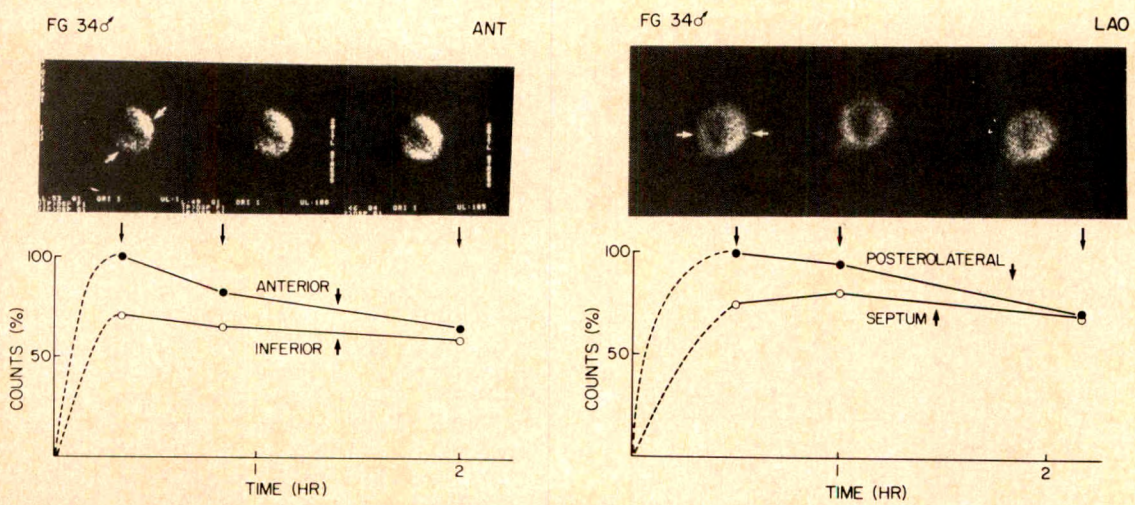

FIGURE 1. Sequential anterior (ANT) and 40° left anterior oblique (LAO) thallium-201 images after exercise and corresponding time-activity curves. Peak activity of 100% refers to the maximum segmental counts recorded during the imaging period. **White arrows** indicate the regions of interest from which the time-activity curves are derived. **Left,** the anterior view shows an initial inferior defect with redistribution on delayed views. **Right,** the left anterior oblique view shows an initial septal defect, which also fills in on delayed views. Right coronary and left anterior descending coronary disease were suspected.

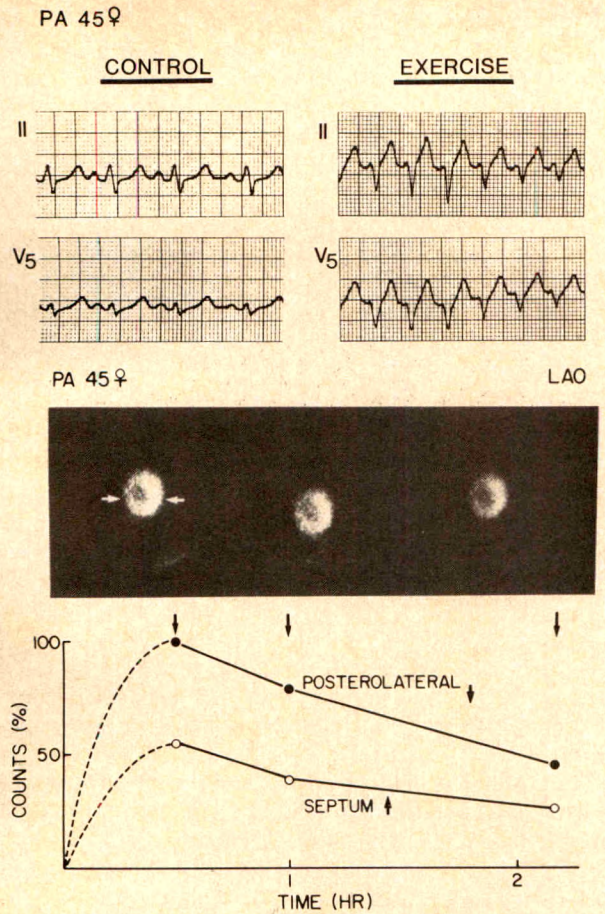

FIGURE 2. Top, control and exercise electrocardiograms in a patient with left bundle branch block. The heart rate increased from 95 to 160 beats/min. **Bottom,** sequential left anterior oblique (LAO) images obtained after exercise and displayed as described in Figure 1 demonstrate a persistent septal defect. Left anterior descending coronary disease was suspected.

17 patients with atypical chest pain had normal exercise Tl-201 scans. Of the 11 patients with abnormal Tl-201 images, 5 had typical angina and 6 had atypical pain. Three patients with typical angina (2 normal Tl-201 studies, 1 abnormal study) had been hospitalized previously with a diagnosis of unstable angina.

Sex: There were 23 women and 18 men in the study group. Seven women and 4 men had abnormal Tl-201 scans. Six women and 5 men had positive exercise electrocardiograms. In this study the specificity of the exercise electrocardiogram and the Tl-201 scan was the same in men and women.

Beta blockade: Twenty-two patients were taking beta-blocking agents (15 propranol, 4 metoprolol, 3 nadolol) and 19 were not. Medication was not stopped before testing. Seven of 11 patients with abnormal Tl-201 images and 15 of 30 with normal images took beta-blocking drugs. Thus, beta-blocking drugs did not influence the specificity of exercise Tl-201 imaging.

Cardiac catheterization: None of the patients had significant CAD. Six patients had 25 to 40% left anterior descending coronary artery lesions. Five of the 6 had normal Tl-201 scans and 1 (25% lesion) had a persistent septal defect. Two of the 6 had positive exercise electrocardiograms.

Thirteen patients had abnormal (>12 mm Hg) resting left ventricular end-diastolic pressure (LVEDP) measured after the "A" wave and before contrast injections. The LVEDP in this group ranged from 16 to 24 mm Hg. Three of these patients had abnormal exercise Tl-201 studies, including the patient illustrated in Figure 1.

Left ventricular wall motion was normal in 38 patients. Two patients had global hypokinesia (ejection fraction 38 and 45%). Their exercise electrocardiograms were normal. One patient had inferior akinesia. Ten of 11 patients with abnormal Tl-201 scans had normal wall motion. The patient with inferior akinesia had right bundle branch block, a nondiagnostic exercise electrocardiogram, and inferior and posterolateral defects.

Ergonovine testing was negative in 7 of 11 patients with abnormal Tl-201 scans. It was not performed in the other 4 patients. Metabolic studies were not performed in our patients.

Miscellaneous findings: Echocardiography was performed in 30 of the 41 patients. Five patients had mitral valve prolapse and 3 of these had Tl-201 scan defects (Table I). One patient with left ventricular hypertrophy on echocardiography had a normal rest and exercise electrocardiogram and Tl-201 scan. There were 2 patients with a history of paroxysmal atrial fibrillation. Both had normal rest and exercise electrocardiograms, but their Tl-201 studies gave abnormal results.

In summary, 9 of 11 patients with abnormal Tl-201 scans had ≥1 cardiac abnormality. Only 13 of 30 patients with normal Tl-201 scans had ≥1 cardiac abnormality ($p < 0.05$).

Discussion

Thallium-201 myocardial perfusion imaging is more sensitive and more specific than exercise electrocardiography in the detection of CAD.[1–3] It is particularly useful for evaluating patients with nondiagnostic or suspected false-positive exercise electrocardiograms.[3,8,9] For these reasons, exercise Tl-201 imaging is frequently used as an important aid in determining which patients with chest pain should be referred for coronary arteriography.

In a group of patients undergoing cardiac catheterization and angiography, we noted an unusually high number of false-positive Tl-201 images (27%). Thus, we have attempted to correlate the clinical and technical factors that may affect the specificity of Tl-201 scintigraphy.

Patient selection: One reason for the relatively low specificity (73%) for CAD in our study may have been patient selection. In previous studies evaluating sensitivity and specificity, exercise imaging was performed in patients referred for cardiac catheterization. In such patients, the prevalence of CAD is usually high. Tl-201 imaging is now used to help select patients for cardiac catheterization. Patients with clinical factors indicating a high probability of CAD or with a positive exercise electrocardiogram or positive Tl-201 scan are referred for catheterization. When chest pain is atypical and

TABLE I Clinical Correlations in 11 Patients With "False-Positive" Thallium-201 Scans

Case	Age (yr) & Sex	Pain	Beta-Blocking Drug	Rest ECG	Exercise ECG	Tl Study	Additional Findings
1	45F	A	+	LBBB	−	S-RD I-RD	. . .
2	47M	T	+	NL	0	I-PD	. . .
3	62F	T	+	NSTA	+	S-PD	. . .
4	68F	A	0	NSTA	0	P-RD	MVP on echo PAF
5	51M	T	0	RBBB	−	I-RD P-PD	Inferior akinesia
6	54F	T	+	NL	0	S-RD AP-PD	MVP on echo
7	34M	T	+	NL	0	S-RD I-RD	LVEDP = 20 mm Hg
8	64F	A	+	NL	+	AN-RD AP-RD	PAF
9	58F	A	+	NL	+	S-PD	LVEDP = 20 mm Hg
10	50F	A	0	NL	−	I-RD AP-RD	MVP on echo LVEDP = 20 mm Hg
11	49M	A	0	RBBB	0	P-PD	. . .

A = atypical; AN = anterior; AP = apical; echo = echocardiogram; I = inferior; LBBB = left bundle branch block; LVEDP = left ventricular end-diastolic pressure; MVP = mitral valve prolapse; NL = normal; ND = nondiagnostic; NSTA = nonspecific T-wave abnormalities; P = posterior; PAF = paroxysmal atrial fibrillation; PD = persistent defect; RBBB = right bundle branch block; RD = redistribution; S = septum; + = positive; 0 = negative; − = nondiagnostic.

adequate exercise electrocardiograms and scintigrams are negative, CAD can reliably be excluded in 94% of patients.[10] Further, Pamelia et al[4] observed only a 2% incidence of subsequent adverse cardiac events in the following 16 months in 351 patients with normal exercise Tl-201 scans. Thus, patients with normal exercise Tl-201 scans are frequently not referred for coronary angiography. Conversely, patients with positive Tl-201 scans may be referred for cardiac catheterization, even in the absence of other evidence of CAD. It is likely that many patients with chest pain, normal coronary arteries, and normal Tl-201 studies were not catheterized, whereas some with positive scans and a low likelihood of CAD were studied, causing our unusually low specificity.

Therefore, it is more appropriate at this time, when evaluating specificity, to use a group of patients with a very low (<2%) pretest likelihood of CAD based on clinical variables and the exercise electrocardiogram.

Clinical characteristics: In this study, a normal exercise Tl-201 study was the most common finding ($p < 0.005$) in patients without significant CAD when compared with other clinical characteristics frequently evaluated in patients with chest pain. Figure 3 summarizes the clinical data in 41 patients with chest pain and without significant CAD.

In the 11 patients with false-positive Tl-201 scans, none of the clinical findings were significantly different. Figure 4 shows that sex, beta-blocker therapy, type of

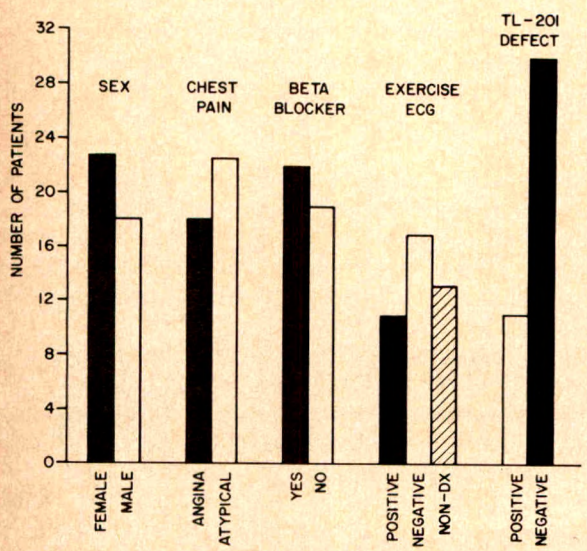

FIGURE 3. Summary of clinical data, exercise electrocardiogram (ECG), and thallium-201 (TL-201) results in 41 patients with chest pain and normal coronary arteries. A negative thallium-201 scan was the most common finding ($p < 0.005$). NON-DX = nondiagnostic.

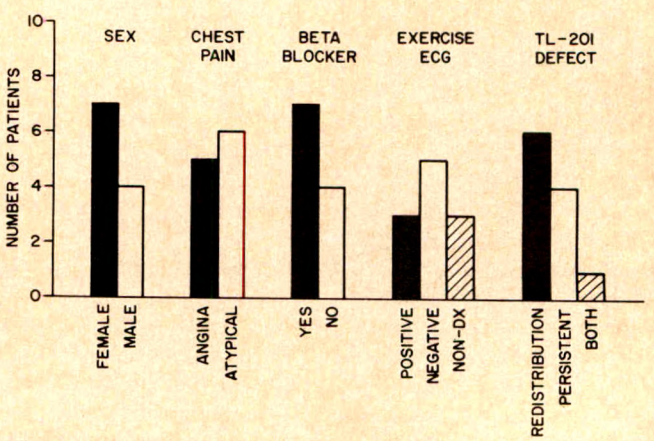

FIGURE 4. Summary of clinical data, exercise electrocardiogram (ECG), and thallium-201 (TL-201) results in 11 patients with false-positive thallium-201 images. None of the factors evaluated correlated with a false-positive thallium-201 study. ECG = electrocardiogram; NON-DX = nondiagnostic.

chest pain, exercise electrocardiogram results, and type of scan defect were not useful in detecting false-positive Tl-201 images.

Friedman et al[11] found the specificity of exercise Tl-201 imaging in women to be 88%. The specificity of the exercise electrocardiogram in women in their study was 41%. In our study, the specificity of Tl-201 imaging in women was lower at 70% (16 of 23), but not significantly different from the specificity in men (78%, 14 of 18). The exercise electrocardiogram in our study was equally specific in men and women (72 versus 74%). Although our results differ somewhat, both Friedman's study and ours demonstrate that exercise Tl-201 imaging is useful in women with chest pain.

A history of classic effort angina pectoris is quite specific for CAD.[12] In our 41 patients, almost half the patients had typical angina and typical angina was present in 45% of the patients with false-positive Tl-201 scans. Other investigators have had similar results.[13]

The effects of beta-blocker therapy on Tl-201 imaging are not clear. Osbakken et al[14] unexpectedly noted an increase in false-positive Tl-201 scans in patients taking propranolol. The mechanism was not explained. This finding was not confirmed in our study or those of others.[15]

Exercise electrocardiogram versus thallium-201 scintigraphy: In this study, the specificity of the exercise electrocardiogram and Tl-201 scintigraphy was the same (73%). However, the number of nondiagnostic exercise electrocardiograms decreased the diagnostic value of the test. It is in patients with nondiagnostic electrocardiograms that Tl-201 imaging may be most useful.[3,8] Interestingly, 3 patients with chest pain (1 typical, 2 atypical) and no significant CAD lesions had positive exercise electrocardiograms and positive Tl-201 scans, a combination that predicts coronary disease in 90% of patients.[16] All 3 patients were women, and all 3 had other cardiac abnormalities, as will be described.

Image interpretation: All exercise Tl-201 images were interpreted by visual inspection of unprocessed raw images as well as by quantitative analysis. This quantitative technique increases the specificity of Tl-201 imaging.[3] Additionally, defects considered to be due to obvious breast shadow or other soft tissue attenuation were not considered abnormal.

Dunn et al[17] reported that it was possible to distinguish false-positive Tl-201 defects by their "inconsistent" nature, that is, isolated apical defects or defects suspected of being due to soft tissue attenuation. However, of their 11 patients with "inconsistent" defects, 5 had scintigraphic evidence of ischemia, manifested by smaller defects on late images. We believe that exercise Tl-201 defects that demonstrate redistribution are usually due to CAD, and others agree that redistribution is usually a highly specific finding.[16] Further, in our patients there was no discernible change in chamber size, which may artifactually produce redistribution.[18]

All 11 of our patients with false-positive scans had defects believed to be consistent with CAD and 3 patients were thought to have 2 vessels involved because of the anatomic distribution of the defects. Thus, in our series, there was no pattern of image defect that reliably predicted a false-positive result.

Cardiac abnormalities: Although there was no significant CAD in our 41 patients, other cardiac abnormalities were frequently detected. Other investigators have detected abnormalities of myocardial flow reserve,[19] lactate production,[20] and abnormal myocardial biopsies[19,20] in patients with chest pain and normal coronary arteries. Some of the patients also had abnormal Tl-201 images.[20] Nine of our 11 patients with false-positive Tl-201 scans had at least 1 cardiac abnormality. Thirteen of 30 patients with normal scans and coronary arteries had a cardiac abnormality ($p < 0.05$).

Mitral valve prolapse: Three of 5 patients with mitral valve prolapse had positive Tl-201 images. Other studies have reported conflicting results of Tl-201 imaging in mitral valve prolapse.[21–23] Although the majority of patients with mitral valve prolapse and normal coronary arteries will have normal exercise Tl-201 images,[21,22] some patients with mitral valve prolapse and abnormal exercise Tl-201 scans have been reported.[23] The metabolic or myopathic abnormalities associated with mitral valve prolapse[24–26] may be the cause of these Tl-201 defects.

Catheterization abnormalities: One of our patients with a 25% lesion of the left anterior descending artery had a persistent septal defect. One patient with inferior and posterior Tl-201 defects had right bundle branch block and inferior akinesia. Coronary artery spasm and subsequent myocardial infarction could explain these findings, but neither patient had electrocardiographic evidence of myocardial infarction and the clinical history did not suggest variant angina. Further, ergonovine testing was negative in 7 patients with abnormal Tl-201 scans, including the 2 just mentioned. Ergonovine testing was not performed in the other 4 patients.

It is also possible that significant coronary stenosis was missed and that the angiogram was falsely negative, particularly in the 3 patients with positive electrocardiograms and Tl-201 scans. Except for the lesions noted, all patients had smooth arteries and no vessels were missing. Additionally, because of the exercise abnormalities, the angiograms were reviewed meticulously, particularly in the distribution of the scan defects. However, this does not exclude nonatherosclerotic forms of ischemia as the cause of the defects. Metabolic studies to evaluate flow reserve and lactate production were not performed.

Electrocardiographic abnormalities: Five of the 11 patients with false-positive Tl-201 scans had abnormalities of conduction or rhythm. Exercise Tl-201 imaging has been suggested as a means to evaluate chest pain in patients with conduction disturbances which render the exercise electrocardiogram nondiagnostic.[3,8] However, other workers have reported an increased incidence of false-positive Tl-201 scans in patients with left bundle branch block.[27] Two of 4 patients had paroxysmal atrial fibrillation and false-positive Tl-201 scans. Both were in sinus rhythm during exercise testing and the cause of the false-positive Tl-201 study remains unclear.

Left ventricular end-diastolic pressure: Thirteen of the 41 patients had abnormally elevated LVEDP. Three of these had abnormal exercise Tl-201 studies. Bush et al[28] report elevated LVEDP in 75 of 125 patients with chest pain and normal coronary arteries. Thirty-three of the 75 patients had angina during catheterization. Nitroglycerin decreased the filling pressure to normal and relieved the angina in all 33 patients. They did not report results of Tl-201 scintigraphy. The mechanism by which abnormal isolated diastolic dysfunction causes chest pain is undefined, but relief by nitroglycerin suggests ischemia may play a role. Similarly, ischemia may also explain Tl-201 image defects in some patients with chest pain, normal coronary arteries, and elevated LVEDP.

Clinical implications: Despite the efforts described to minimize the number of false-positive Tl-201 studies, a number of patients with chest pain and angiographically normal coronary arteries will demonstrate Tl-201 image defects. A normal exercise Tl-201 myocardial perfusion study is the most useful predictor of normal coronary arteries in patients with chest pain. Other clinical variables are not as helpful. However, patients with chest pain and normal coronary arteries frequently have other cardiac abnormalities that may represent nonatherosclerotic forms of ischemia or abnormal myocardial cellular metabolism. Such patients may have abnormal Tl-201 scintigrams.

The use of exercise Tl-201 imaging as a screening method in patients with chest pain will undoubtedly increase. This will probably result in the detection of increasing numbers of patients with abnormal Tl-201 images and normal coronary arteries. The high prevalence of cardiac abnormalities other than CAD in our study suggests that the true specificity of exercise Tl-201 imaging is undetermined and depends on the definition used.

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Natural History of Platelet Deposition on Dacron Aortic Bifurcation Grafts in the First Year After Implantation

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This study defined the dynamics of platelet deposition on Dacron® arterial grafts up to 1 year after implantation in human subjects. Indium-111 platelet imaging was performed on 8 men 1 to 2 weeks after graft implantation and on 5 of these patients at a mean of 31 weeks (range 28 to 34) and again at 55 weeks (range 50 to 62). Serial imaging was performed at 24 to 96 hours after platelet labeling and injection in each study. Quantitative analysis was performed using a graft/blood ratio that compared background-corrected indium-111 platelet activity in the graft region to whole-blood indium-111 platelet activity. Additionally, blinded qualitative visual analysis of the images compared graft activity with the activity in adjacent native arteries. The mean of all graft/blood ratios (24, 48, 72, and 96 hours) progressively decreased from 4.4 ± 2.1 (±1 standard deviation) at 1 to 2 weeks to 3.0 ± 1.8 at 31 weeks ($p = 0.002$). There was no further decrease at 55 weeks (2.8 ± 2.0). For comparison, 12 normal subjects without grafts had a mean ratio of 1.8 ± 0.7. Visual analysis detected platelet deposition in 7 of 8 grafts at 1 to 2 weeks, 4 of 5 at 31 weeks, and 4 of 5 at 55 weeks. Deposition decreased qualitatively in 2 of 5 patients at late study. It is concluded that there is consistent, early platelet deposition on Dacron grafts in man. Although deposition decreases over 31 weeks, it remains readily detectable in most patients at 1 year. These findings suggest absent or incomplete endothelialization of the graft flow surface in humans in the first year after implantation.

The platelet response to recently implanted Dacron® arterial prostheses in humans has not been completely defined. In several animal models, platelet deposition occurs frequently in recently implanted prosthetic grafts,[1–7] but is rarely noted in chronically implanted grafts.[5,7–9] In animals, this decrease in platelet deposition over time is presumably due to the progressive endothelial coverage of the graft flow surface that occurs after implantation.[2,3,5–12] Experimental support for this hypothesis has come from studies in baboons and in dogs in which progressive endothelial coverage of the flow surface of Dacron grafts correlated well with normalization of platelet survival.[2,3]

In human subjects with recently implanted grafts, platelet survival times are decreased at 2 to 4 weeks after graft implantation, but normalize by 9 months.[3,13] However, the recent findings that indium-111–labeled platelet accumulation is detectable on chronically implanted Dacron grafts in patients indicates that platelet deposition continues beyond the period of shortened platelet survival, although possibly at a lesser rate.[14–18] This study quantitates the platelet deposition response to recently implanted Dacron aortic bifurcation grafts in human subjects and determines whether deposition decreases in the first year after implantation.

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Methods

Subjects: Eight men, mean age 56 years (range 47 to 65), were studied. All had DeBakey knitted Dacron aortic bifurcation grafts placed with standard vascular surgical techniques. One patient received dextran 40 (50 ml/hour) for 48 hours postoperatively. The other subjects received no anticoagulants or platelet inhibitory drugs (including aspirin, dipyridamole, sulfinpyrazone, ibuprofen, and other nonsteroidal anti-inflammatory agents) during the period of study. No patient had clinically apparent peripheral emboli or graft occlusion during follow-up study.

All 8 subjects were initially studied 1 to 2 weeks postoperatively. Five subjects returned for repeat studies a mean of 31

weeks (range 28 to 34) and again at 55 weeks (range 50 to 62). Three patients were not restudied: 1 refused, 1 moved, and 1 could not be located. This study was approved by the University of Washington Human Subjects Review Committee. All subjects gave informed consent.

Platelet labeling, imaging and analysis: Autologous platelets were labeled with indium-111 oxine using a closed blood bag modification of the technique of Thakur et al[19] as previously described.[20] The initial centrifugation (350 g × 15 minutes) and subsequent centrifugations (1,300 g × 15 minutes) have been changed since the original description. The mean labeling efficiency for all 18 studies was 34 ± 10% (±1 standard deviation), which is lower than that reported in studies using open test-tube labeling methods,[19,21] presumably due to loss of the label in the interstices of the plastic blood bags. The mean injected dose did not significantly differ between the 3 serial study times (352 ± 33, 339 ± 33, and 257 ± 177 μCi, respectively). For all 18 studies, the mean percentage of indium-111 activity free in the plasma at 24, 48, 72, and 96 hours after labeled platelet injection was 5 ± 4%, 4 ± 2%, 6 ± 2% and 9 ± 4%, respectively.

The graft was imaged by taking an anterior view of the lower abdomen that largely excluded the liver and spleen for 150,000 counts, typically at 24, 48, 72, and 96 hours after labeled platelet injection.[14] Imaging was discontinued at 72 hours in 5 studies (4 initial studies and 1 at 55 weeks) and at 96 hours in 13. Images were recorded on Polaroid® trilens film for visual assessment of the unprocessed data and on a computer disc system with a 128 × 128 matrix to allow quantitation of platelet deposition. Qualitative visual analysis of the unprocessed images from all 18 graft studies, in addition to 12 previous studies from normal subjects without grafts,[14] was performed by 2 observers who were unaware of the clinical data or the study sequence. Images were defined as showing platelet deposition if there was one or more areas of activity present in the region of an aortic bifurcation graft that was clearly greater than the large vessel blood pool activity present above or below the area encompassed by a graft. Studies were graded as positive, negative, or equivocal for platelet deposition. On serial studies, a decrease in platelet deposition was defined as conversion of a positive study to either negative or equivocal.

Quantitative analysis of the platelet image data was performed using a graft/blood ratio that compared activity in the graft region to well-counted whole blood indium-111 platelet activity.[14] This ratio was determined for each patient at each imaging time. In 2 studies (both in the same patient studied at 2 and 34 weeks after graft implantation), graft/blood ratios could not be calculated because the patient refused to have serial venipunctures to obtain whole blood samples (2-week study) and because of a computer malfunction (34-week study). For purposes of comparison, the graft/blood ratios of young normal subjects without grafts are also presented; the data in normal subjects has been previously reported.[14] Statistical analysis was by paired or unpaired t testing. All values are expressed as mean ± standard deviation.

Results

Quantitative analysis (graft/blood ratio): As shown in Table I, there was a decline in the graft/blood ratios at the 24, 48, 72 and 96-hour imaging times from the initial to late studies. Among the 4 subjects who had 72-hour graft/blood ratios obtained at all 3 study times, the decrease from the early to middle to late studies was from 4.9 ± 2.2 to 3.3 ± 2.1 ($p = 0.07$) to 2.9 ± 2.0 ($p = 0.01$). Additionally, the mean of all graft/blood ratios obtained at all serial imaging times (24, 48, 72, and 96 hours) significantly decreased from the first study (4.4 ± 2.1) to the second study (3.0 ± 1.8, $p = 0.002$), implying a decrease in deposition. There was no further significant decrease from the second to the third study (2.8 ± 2.0) ($p = 0.001$ versus Study 1) (Fig. 1). For comparison, normal subjects had a mean value of 1.8 ± 0.7 for all graft/blood ratios. All patients with grafts had a decrease in the graft/blood ratio of at least one third

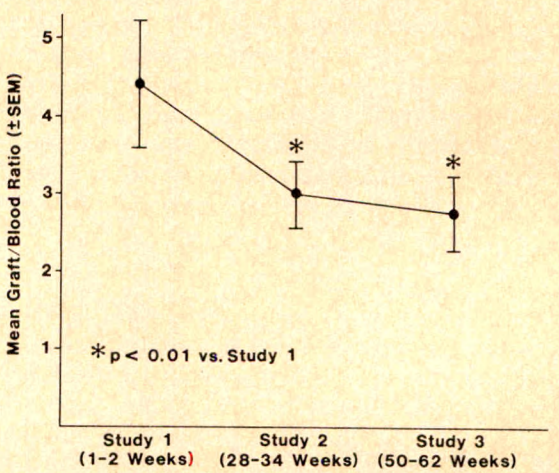

FIGURE 1. Platelet deposition on Dacron grafts in the first year after implantation. The mean of all graft/blood ratios (24, 48, 72, and 96 hours) significantly decreased from Study 1 to Study 2 ($p = 0.002$). There was no further significant decrease from Study 2 to Study 3. These results imply a decrease in deposition within the first 31 weeks after implantation.

TABLE I Graft/Blood Ratios

	Hours			
	24	48	72	96
Study 1 (1–2 weeks)				
All patients	2.4 ± 1.1	3.2 ± 1.3*	4.3 ± 2.2*	5.6 ± 3.5*
Patients with serial studies	3.0 ± 1.1	4.1 ± 1.3*	4.9 ± 2.2*	7.0 ± 3.5*
Study 2 (28 to 34 wk)	2.1 ± 0.8	2.3 ± 1.3	3.3 ± 2.1	3.5 ± 2.2*
Study 3 (50 to 62 wk)	1.9 ± 1.0†	2.7 ± 1.8	2.9 ± 2.0†	3.4 ± 2.1*
Normal subjects	2.0 ± 0.7	1.8 ± 0.5	1.7 ± 0.8	1.7 ± 0.9

* $p < 0.05$ versus normal subjects at a single imaging time.
† $p < 0.05$ versus Study 1 at a single imaging time.

TABLE II Visual Results

Case	Study 1 (1 to 2 wk)	Study 2 (28 to 34 wk)	Study 3 (50 to 62 wk)
1	+	EQ	−
2	+	+	EQ
3	+	+	+
4	+	+	+
5	+	+	+
6	+	ND	ND
7	+	ND	ND
8	−	ND	ND

+ = positive study; − = negative study; EQ = equivocal study; ND = not done.

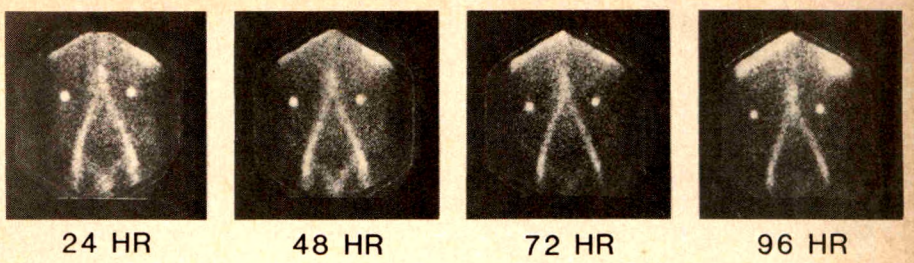

FIGURE 2. Diffuse platelet deposition is present throughout this Dacron aortic bifurcation graft 2 weeks after implantation. From 24 to 96 hours after labeled platelet injection, background blood pool activity decreases due to platelet senescence, while graft area activity remains intense.

on either the 72- or 96-hour image from the initial to the final study. However, despite the decline in the mean graft/blood ratio, patients with 1-year-old grafts continued to have a higher mean ratio than normal subjects ($p = 0.003$).

Visual analysis (Table II): On visual analysis, none of the 12 normal subjects had abnormal platelet deposition. In contrast, 7 of the 8 patients with grafts had detectable platelet deposition 1 to 2 weeks after surgery (Table II). All 5 patients who had serial studies had a positive result on initial study (Fig. 2). Of the 5 subjects studied at 31 ± 3 weeks and at 55 ± 5 weeks, results in 3 remained positive at both late studies. Of the other 2 subjects studied serially, 1 had only equivocal deposition at 28 weeks and no detectable deposition at 50 weeks and the other had a persistently positive study at 34 weeks but an equivocal study at 51 weeks (Fig. 3). Thus, 2 of 5 subjects had a visually detectable decrease in deposition at late study periods, although at both late studies, 4 of 5 subjects still had positive or equivocal images.

Discussion

This study documents that platelet deposition on Dacron grafts in humans is detectable in the early period after graft implantation and remains detectable in most patients studied 1 year later. Qualitative visual analysis detected deposition in 7 of 8 grafts studied 1 to 2 weeks after implantation and in 4 of 5 (3 positive and 1 equivocal) studied at 1 year. The visual results early postoperatively are similar to previous reports in which visually detectable deposition was present in recently implanted Dacron extracardiac conduits[22] and in recently implanted Dacron aortic bifurcation grafts.[18,21] The visual results at 1 year confirm our earlier findings of platelet deposition in 13 of 15 chronically implanted Dacron grafts.[14] It thus appears that most Dacron grafts in human subjects have detectable platelet deposition for long periods of time after implantation.

Whereas the qualitative visual data suggested that deposition diminished over time in 2 of the 5 subjects studied serially, the quantitative analysis suggested that deposition diminished in all subjects. Most, if not all, of the decrease in deposition occurred within the first 31 weeks after implantation; the graft/blood ratio did not significantly decrease further from the 31-week study to the 55-week study. These results are in agreement with those reported by Goldman et al[17,18] in similar groups of patients. They also found that deposition remained readily detectable at late study but that the rate of platelet accumulation diminished from early postoperatively to 6 to 12 months later. Their quantitative method assessed only the rate of platelet deposition determined over an 8-day period from limited regions of the graft, and thus their results are not strictly comparable to ours, which allow comparison of both the magnitude of deposition throughout the entire graft as well as the rate of deposition from 1 study to another. Our study documents a decrease in both the rate and magnitude of platelet deposition in the first year after implantation.

The finding of decreased platelet deposition over time is consistent with platelet survival studies. Platelet survival, which was not measured in the current study, has been found to be reduced in the first several months after placement of an arterial graft, but normalizes by 9 months to 1 year after implantation.[3,13] An increase in platelet survival would not affect our quantitative results because such an increase would equally affect both the numerator and the denominator of the graft/blood ratio and, thus, result in no change in this measurement of graft platelet deposition. Our findings document that the normalization of platelet survival that occurs in patients with grafts does not indicate cessation of platelet accumulation on the graft, because deposition remained detectable by both visual and quantitative analysis. Platelet imaging, by analyzing a specific localized site of platelet deposition, may be more sensitive for the detection of platelet accumulation than the platelet survival time, which reflects the entire circulating platelet pool.

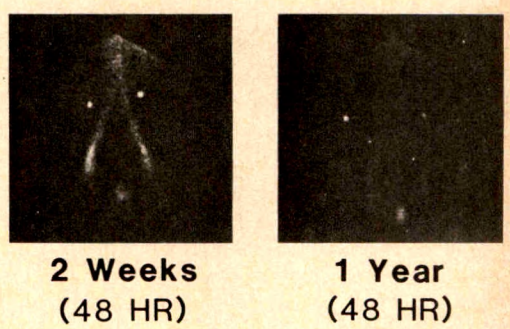

FIGURE 3. Diffuse platelet deposition was present in this Dacron aortic bifurcation graft 2 weeks after implantation (**left**) but was not detectable 1 year later (**right**). Both images were obtained 48 hours after labeled platelet injection.

The increase in the mean graft/blood ratio from 24 hours to 96 hours in both early and late postoperative studies implies progressive deposition of labeled platelets or labeled platelet products on the prosthetic flow surface over a 4-day period. Eventually, an equilibrium must be reached between platelet deposition and removal. Our data indicate that such a steady state is not reached in the first 96 hours after labeled platelet injection. These results confirm our earlier findings in 15 patients with chronically implanted Dacron grafts[14] and findings in a baboon model of implanted Dacron prostheses.[1]

It is possible that our results at the initial study would have been more dramatic had patients been labeled earlier postoperatively, because the peak platelet deposition rate may occur very shortly after graft implantation. The initial studies were done at 1 to 2 weeks because patients were clinically stable at that time and because active bleeding into the operative site, which would invalidate the results, could be excluded.

Detectable platelet deposition on Dacron-blood interfaces implies incomplete or ineffective graft endothelial cell coverage. Our findings of deposition on acute and chronic grafts are consistent with the limited data regarding the histology of grafts implanted in human subjects. These studies have rarely documented endothelial cell coverage[8,23–29]; however, the same studies for the most part did not note significant platelet deposition, and it is possible that the fixation techniques required to preserve platelet and endothelial cell morphology were inadequate. Data in human subjects contrast with animal studies in which endothelial cell coverage of the graft flow surface and decreasing platelet deposition occur over time.[2,3,5–12] This apparent disparity between the human and animal response to prosthetic materials suggests that studies of prosthetic materials in animals should be extrapolated to human beings only with caution.

Berger and Salzman[30] noted that inadequate measures for assessing the thrombogenicity of prosthetic materials in patients have impeded the development of improved materials. Platelet imaging, which is noninvasive, repeatable, organ specific and quantifiable, may provide an additional means of assessing prosthetic thrombogenicity in man. Less reactive prosthetic materials should lead to a visual and quantifiable decrease in platelet deposition both initially and on longitudinal study. In addition, as has been suggested in animal models, platelet imaging may be helpful in assessing whether platelet inhibitory or anticoagulant drugs can decrease thrombus formation on prosthetic surfaces.

This study demonstrated consistent early platelet deposition on Dacron grafts in human beings. Although deposition decreases over 31 weeks, it remains readily detectable in most patients at 1 year. These findings suggest absent or incomplete endothelial coverage of Dacron graft flow surfaces in human subjects in the first year after implantation.

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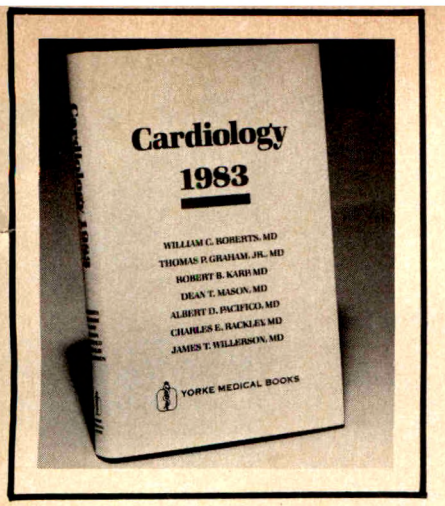

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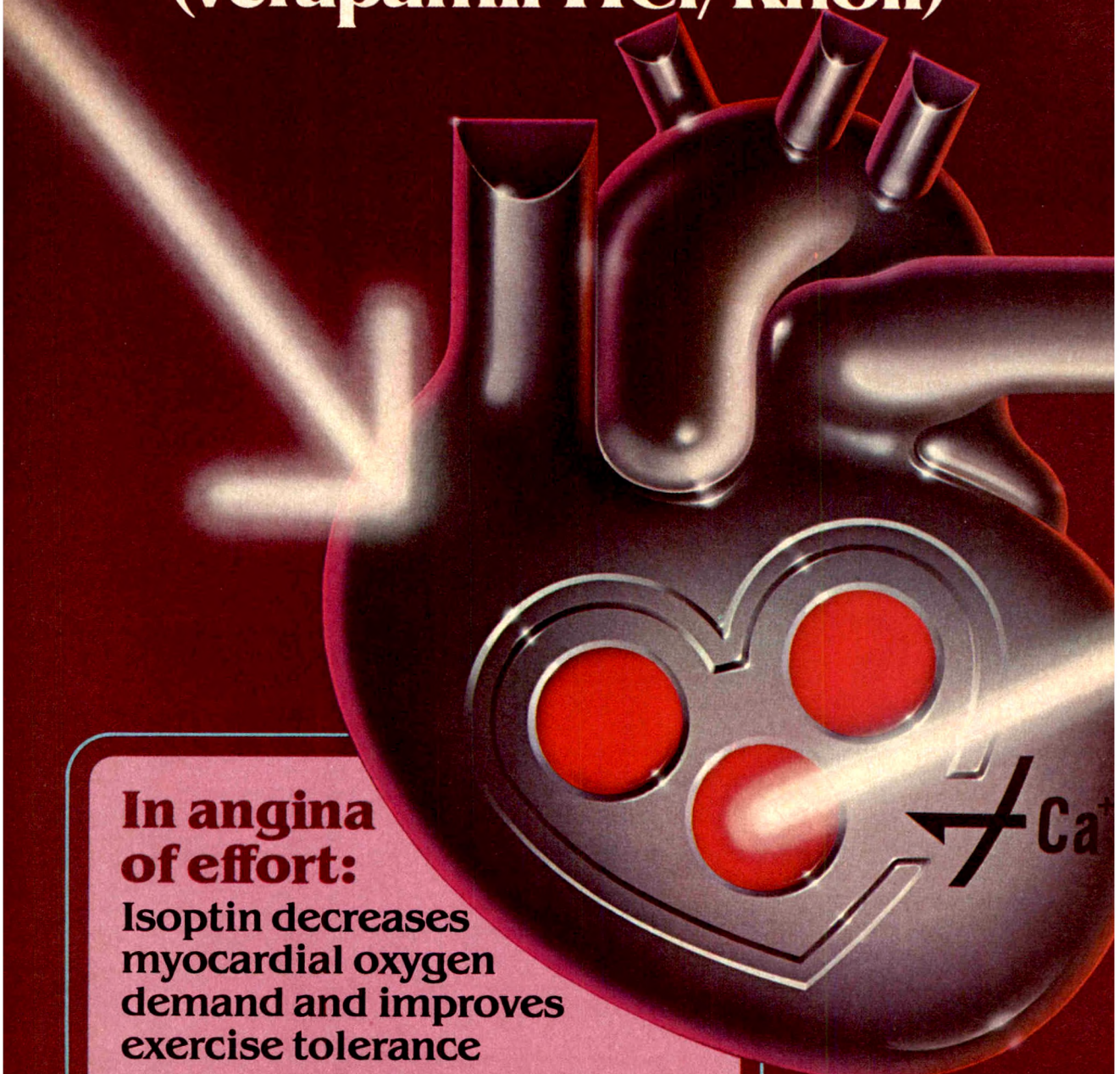

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068

References: **1.** Frishman WH, Klein NA, Strom JA, et al: *Circulation* 65 (suppl I): 151-159, 1982. **2.** Leon MB, Rosing DR, Bonow RO, et al: *Am J Cardiol* 48:131-139, 1981. **3.** Bala Subramanian V, Bowles MJ, Davies AB, et al: *Am J Cardiol* 49:125-132, 1982. **4.** Data on file, Knoll Pharmaceutical Company. **5.** Parodi O, Maseri A, Simonetti I: *Br Heart J* 41:167-174, 1979. **6.** Johnson SM, Mauritson DR, Willerson JT, et al: *N Engl J Med* 304:862-866, 1981. **7.** Johnson SM, Mauritson DR, Corbett JR, et al: *Am J Med* 71:433-451, 1981. 2067

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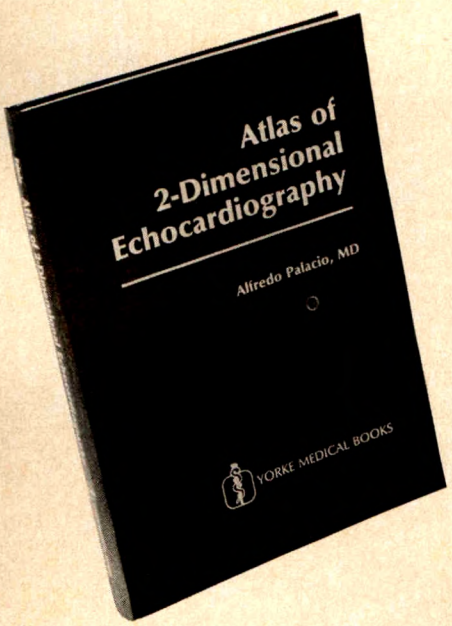

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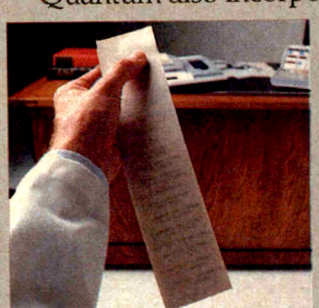

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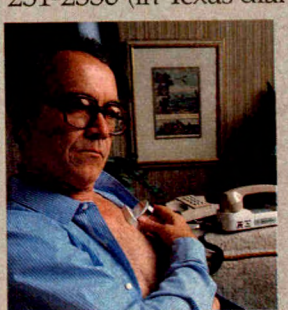

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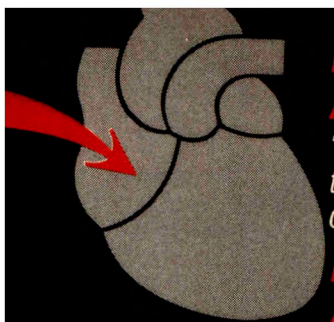
QUANTUM INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacing are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include, but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting such symptoms as intractable, recurrent arrhythmias, and who have been shown to benefit from temporary cardiac pacing, are considered candidates for permanent cardiac pacing.

The indications for permanent pacing in cases of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, the mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias that impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no know contraindications to the use of pacemakers as a medical method for control of heart rate.



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"Quinidine remains the drug of choice to prevent recurrence of atrial fibrillation or flutter."[1]

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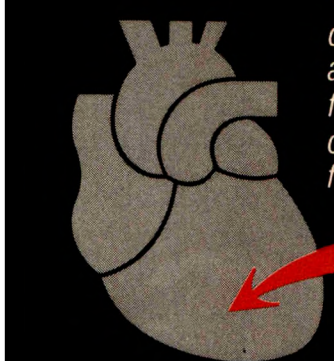
"Quinidine is one of the most useful drugs for chronic treatment of ventricular arrhythmias . . . or for the prevention of ventricular fibrillation."[2]



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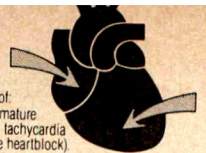

INDICATIONS AND USAGE:
Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
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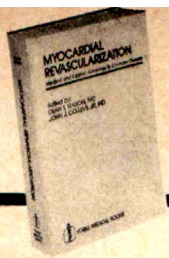

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Systematic Analysis of Contrast Echocardiograms

RICHARD S. MELTZER, MD, ZVI VERED, MD, JOS ROELANDT, MD, and HENRY N. NEUFELD, MD

Contrast echocardiography was first described in 1968. Since then, many reports have described clinical and experimental uses for the technique. Contrast echocardiography is performed at least occasionally in most echocardiography laboratories, but most physicians use this technique merely to determine the presence of a shunt or, more rarely, for structure identification. Contrast echocardiography can provide much more information. Some different types of information available from con echocardiographic records are discussed, inclu timing of contrast appearance within the ca cycle, relative timing of appearance in diff cardiac structures, relative intensity of con opacification, cyclical changes in contrast op cation, negative contrast effect, slope of con trajectories on M-mode contrast echocardiogra and clearance times.

In 1968, Gramiak and Shah[1] first reported the contrast echocardiographic effect achieved by injecting idocyanine green contrast material in the heart during echocardiography. They credited Joyner as the discoverer of the effect. Since then, the literature on contrast echocardiography has grown and the subject has been extensively reviewed.[2–11] Although most echocardiographic laboratories use contrast echocardiography at least occasionally,[12] there is room for further organized thinking about systematic analysis of contrast echocardiograms to maximize their diagnostic potential, in a manner analogous to systematic inspection of a chest X-ray or M-mode echocardiogram to insure that a maximum of diagnostic information is obtained from the study. Some physicians are unaware of the amount and type of information inherent in a contrast echocardiogram. This report points out the types of information available from systematic analysis of contrast echocardiograms.

Timing of Onset of Contrast Appearance

With respect to the cardiac cycle: Contrast material frequently enters an echocardiogram fairly suddenly, within a small fraction of a cardiac cycle. The timing of this entry may be reproducible even if the peripheral intravenous injection technique is quite variable. This phenomenon is used diagnostica detect tricuspid regurgitation when imaging the in vena cava (IVC) echocardiographically.[13–15] If th rograde flow of contrast material enters the IVC sl after atrial contraction, tricuspid regurgitation i likely. Tricuspid regurgitation is diagnosed if it e the IVC shortly after the onset of the v-wave on the atrial pressure tracing (or jugular or IVC pulsati

Atrial septal defect (ASD) is usually distingu from ventricular septal defect (VSD) on cor echocardiography by the position and direction abnormal contrast flow. There are also some more s differences of timing of contrast appearance. In contrast material enters the left ventricle in dia after the mitral valve has been opened. Caref spection of contrast echocardiograms will demon that the first appearance of contrast material in th ventricle across an uncomplicated VSD is earlier, d ventricular relaxation before the mitral valve o because this is when a small right-to-left gradient in a predominantly left-to-right shunting VSD.[16] I timing the entry of contrast material into the lef tricle after peripheral intravenous injection has proposed[17] as a method of roughly quantifying th modynamics across a VSD: patients with pressu the right ventricle <60% of left ventricular pre usually do not have contrast echocardiographic s ing unless ventricular premature contractions Those with right ventricular pressure in the range to 80% of left ventricular pressure and a pulmo systemic flow ratio (Q_p/Q_s) from 2.0 to 5.0 had ap ance of the left ventricular contrast material d relaxation, but the contrast material returned t right ventricle during mid- and late diastole, s

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none remained in the left ventricle at the onset of systole and thus none was ejected into the aorta (Fig. 1). A third pattern was found in patients with systemic right ventricular pressures and a Q_p/Q_s >3:1. In these patients, contrast material initially appeared in the left ventricle at the same time in the cardiac cycle as in the previous group, but it remained in the left ventricle through systole and was ejected into the aorta. A fourth pattern was found in patients with significant pulmonary stenosis, systemic right ventricular pressures, right-to-left shunting, and a Q_p/Q_s ranging from 0.4 to 0.8. The appearance time of contrast material in the left ventricle was distinctly earlier in the cardiac cycle than for the previous group. As in the previous group, the contrast material remained in the left ventricle throughout diastole and was ejected into the aorta on the next systole. A fifth pattern was found in 3 patients with Eisenmenger physiology and pulmonary vascular resistance >15 U/m^3. In these patients, entry of contrast material into the left ventricle was still earlier in the cardiac cycle than that in patients in the third and fourth group. The investigators concluded that timing of contrast entry into the left ventricle after peripheral intravenous injection yields important information about the hemodynamics and shunting across a VSD.

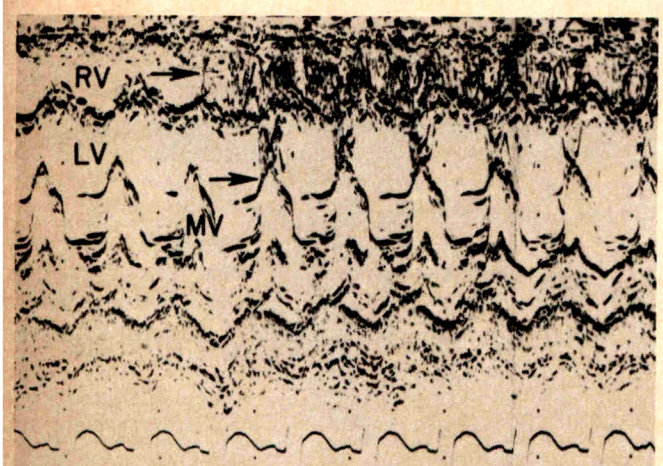

FIGURE 1. Echocardiographic study from a patient with a right ventricular/left ventricular pressure ratio of 0.7. The initial appearance of contrast within the right ventricle (RV) is indicated by the **upper arrow.** The appearance of contrast anterior to the mitral valve (MV) in the LV is indicated by the **lower arrow.** During late ventricular filling, contrast returns completely to the RV, with none persisting in the LV during ventricular systole. (Reproduced, by permission, from the American Heart Association.[17])

With respect to different cardiac chambers: In ASD, contrast material injected into a peripheral vein is first seen in the right heart and then crosses into the left heart within the following 1 to 3 cycles. If contrast material is first imaged in the left heart 10 to 12 cardiac cycles after entry into the right heart, intrapulmonary rather than intracardiac shunting is suggested.[18] This delay ranges from 0 to 5 cardiac cycles (mean 1.5) in patients with ASD and from 2.5 to 10 cardiac cycles in patients with pulmonary arteriovenous fistula.[19] Thus, patients with intracardiac shunting can usually be distinguished from those with intrapulmonary shunting on the basis of the relative timing of arrival of contrast material in the left heart, although there may be an overlap between the 2 groups for a relative arrival delay of about 3 to 5 cardiac cycles (Fig. 2).

The sequence of opacification of the cardiac chambers and great vessels provides information on intracardiac flow similar to that available from angiographic or radionuclide studies, but unavailable by other echocardiographic means including Doppler echocardiography.

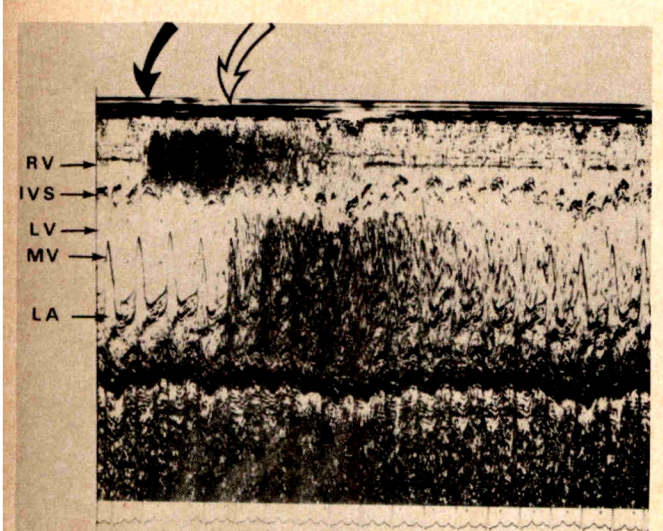

FIGURE 2. Contrast echocardiogram after intravenous injection in a patient with a pulmonary arteriovenous fistula. Initial opacification of the right ventricle (RV) is indicated by the **upper solid arrow.** Opacification of the left atrium (LA) and left ventricle (LV) 3 cardiac cycles later is shown by the **open arrow.** IVS = intraventricular septum; MV = mitral valve.

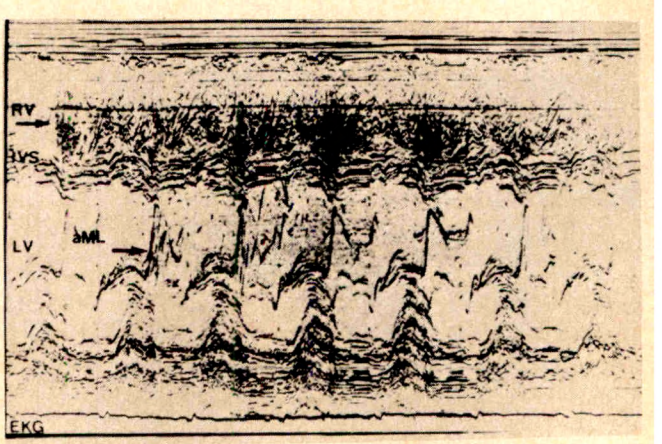

FIGURE 3. M-mode echocardiogram after peripheral venous injection of 5% dextrose in a patient with atrial septal defect. During the fourth and fifth diastoles in the tracing, the contrast is relatively more intense in the right ventricle (RV) and less intense in the left ventricle (LV) than in the beats immediately before and after. The reason is a lessening of the right-to-left shunt during inspiration. aML = anterior mitral leaflet; EKG = electrocardiogram; IVS = intraventricular septum.

This information is particularly important in complex congenital heart disease.[4,20,21]

Relative Intensity of Contrast Opacification

Frequently, different cardiac chambers opacify to a markedly different extent. Echocardiographers soon realized that relative opacification did not convey information about the size of an ASD, but this concept is misleading. It would be unreasonable to expect useful diagnostic information on the size of a left-to-right shunt by looking at the magnitude or timing of right-to-left shunting,[22] and this is why left-sided cardiac opacification after intravenous injection conveys no information about the significance of most ASDs (without pulmonary hypertension). However, the relative intensity of contrast opacification is a rough guide to the degree of relative filling in the direction of the shunting; that is, most patients with ASD show greater relative contrast opacification of the right ventricle compared with the left ventricle because flow from the contrast-filled right atrium preferentially enters the right ventricle rather than the left atrium. When pulmonary hypertension and Eisenmenger physiology occur, this situation changes and the equal intensity of left-sided cardiac opacification relative to the right heart suggests this diagnosis.

Occasionally the negative contrast effect of unopacified blood entering the right atrium from the left atrium is quite striking. However, considerable experience is necessary to reliably distinguish a negative contrast effect due to abnormal flow across an ASD from the normal inferior vena cava and coronary sinus flow. In our experience, a negative contrast effect is not a sensitive sign, either.

Figure 3 is an example of how relative contrast density can give clues to underlying physiologic phenomena. This M-mode echocardiogram was taken after peripheral intravenous contrast injection in a patient with ASD. During inspiration, the relative contrast density is greater on the right side and less on the left, indicating a decrease of right-to-left shunting at this phase of the respiratory cycle.

In patients with complex congenital disease, the great vessel receiving most of the systemic venous return can be identified as the one with the relatively greater opacification after intravenous injection. This important use of relative intensity is quite helpful in the analysis of patients with transposition of the great arteries: although the anteroposterior relations of the great arteries in this group of patients are quite variable from the precordial transducer position, on suprasternal studies the superior great vessel (closer to the transducer) is the aorta. Therefore, if the relative intensity in this vessel is greater than that in the pulmonary artery below it, the echocardiographer can deduce that most of the systemic venous return is reaching the aorta, suggesting the presence of transposition with insufficient intracardiac mixing of pulmonary and systemic venous return.[23] This situation should change toward a more equal relative contrast intensity after successful Rashkind balloon atrial septostomy.

Clearance Time

It is easier to define the concept of clearance time theoretically than to apply the definition practically. Clearance time is the length of time or number of cardiac cycles necessary for contrast material to be cleared from a particular cardiac chamber or great vessel after its initial appearance. The problem in application of this definition is that the end point is not well defined: contrast decays exponentially in most situations, and exactly where to place the end is frequently difficult. There are 2 approaches to arbitrarily aid in clinical research using clearance times: (1) Take the last cardiac cycle where an arbitrary number—perhaps 5—of definite contrast images is seen as the end point. (2) Sidestep the problem of definition of an exact end point entirely by statements such as, "Contrast remained in the chamber >20 cardiac cycles," or "All normal subjects showed clearing of contrast in <10 cardiac cycles." Another problem with using clearance time clinically is the lack of reproducibility in contrast echocardiographic injections; an injection with more intense contrast or slower contrast delivery may also take longer to clear than one with a smaller contrast bolus.

Both low cardiac output and regurgitation of a valve immediately proximal or distal to a chamber or vessel would be expected to increase the clearance time of contrast material within that chamber or vessel. Clearance time has been reported prolonged in 1 clinical example of each: Tsuyuguchi et al[24] recently suggested that prolonged clearance time of contrast in the right ventricle indicates right-sided heart failure, and it has been suggested that tricuspid regurgitation is severe when clearance time of contrast material in the inferior vena cava after upper extremity intravenous injection exceeds 20 cardiac cycles (S. Castellanos, MD, Athens, Greece, personal communication).

Another use of clearance time is to examine the relative clearance time of 2 different cardiac chambers or vessels. In transposition of the great arteries, the aorta receives most of the systemic venous return and is thus opacified more intensely and persistently than the pulmonary artery after an intravenous contrast injection. Hunter and Sutherland[25] state that when there is minimal interatrial mixing and aortic saturation is <40%, the aorta is opacified more than twice as many cycles as the pulmonary artery. As mixing improves at the atrial level and the aortic saturation is 40 to 60%, the pulmonary artery opacifies more than half as many cycles as the aorta, although there is usually still differential opacification. When mixing is adequate and aortic saturation is >60%, both great arteries have similar contrast clearance times; if the clearance times cannot be distinguished at all, there is usually <10% difference in aortic and pulmonary artery saturation.

Videodensity Analysis

A proposed method to quantify contrast appearance and clearance on 2-dimensional echocardiography is to examine the videodensity decay from a selected cham-

ber or vessel. This method has been reported capable of quantifying cardiac output[26] and shunts in the direction of contrast flow ("positive" contrast rather than "negative" contrast).[27,28] We have found variability of videodensity decay constants to be an important problem[29] and look to the availability of a more reproducible contrast agent before this technique can attain clinical value.

Echocardiographic contrast can be used with 2-dimensional echocardiography to assess myocardial perfusion in experimental animals,[30,31] and videodensity determinations have been reported to correlate with measurement of myocardial blood flow by radioactive microspheres.[32]

Slope of Contrast Trajectories on M-Mode Echocardiograms

Assuming that microbubbles of air are the source of contrast,[33] the slope of an individual contrast trajectory on an M-mode tracing is the component of the velocity of that microbubble projected in the direction of the ultrasonic beam, toward or away from the transducer (Fig. 4). Both qualitative information (motion toward or away from the transducer depending on whether the slope is positive or negative, respectively) and quantitative information (the absolute value of this velocity in cm/s) are thus available from systematic analysis of contrast trajectory slopes. Using Doppler echocardiography as a reference, we[34] recently verified that the velocity measured from M-mode slopes closely correlates with the velocity measured from the Doppler shift in the pulmonary artery and across the tricuspid valve in a group of normal volunteers. In fact, there are many similarities between measuring velocities by Doppler or analyzing M-mode contrast slopes, mainly because they both measure the same component (along the ultrasonic beam) of the 3-dimensional velocity vector. Other similarities and relative advantages of each technique are listed in Table I. Shiina et al[35] recently showed that M-mode contrast slopes correlate with invasive measurements of blood velocity across the tricuspid valve and pulmonary artery, and that velocities measured from contrast slopes change as expected with simple interventions. Valdes-Cruz et al[36] have cautioned that microbubble velocity is not necessarily the same as blood velocity.

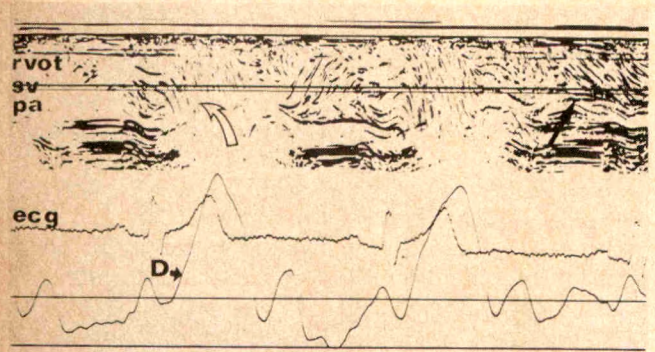

FIGURE 4. M-mode echocardiogram (**upper tracing**) of the right ventricular outflow tract (rvot) and pulmonary artery (pa) after peripheral intravenous contrast injection. The simultaneous mean Doppler velocity signal (D, **lower tracing**) is sampled at sample depth (sv) on the M-mode tracing. The Doppler tracing is inverted so that velocities away from the transducer are portrayed as positive deflections. Higher velocities away from the transducer are seen during systole (**open arrow**) both as steeper contrast slopes and as a higher Doppler velocity. During diastole (**closed arrow** on right) the slope of contrast in the sv approaches 0, as does the Doppler signal. ecg = electrocardiogram.

TABLE I Echocardiographic Velocity Measurements: Doppler Versus M-Mode Contrast Slope

Similarities
Both look at the component of blood velocity along the echocardiographic beam direction (towards or away from the transducer)
The same transducer may be used for both studies
Advantages of M-mode contrast echocardiography
Not limited by distance from target or maximum velocity that can be detected
Samples many depths simultaneously (only multigate or continuous wave Doppler instruments do this)
Uses less expensive, more generally available equipment (only M-mode instrument and intravenous line needed)
Advantages of Doppler echocardiography
Entirely noninvasive
Can sample left heart velocities in absence of shunt
More clinical experience available with this technique than with M-mode slope analysis
Measures blood velocity rather than microbubble velocity

Because velocity analysis from M-mode contrast slopes is newly reported, there are as yet few clinical studies using this technique. Those already reported are largely qualitative, using direction toward or away from the transducer to diagnose flow abnormalities on the right side of the heart in pulmonary regurgitation[37] and pulmonary hypertension.[37,38] An example of the use of contrast echocardiography to diagnose pulmonary insufficiency is shown in Figure 5. Although it is too early to determine if quantitative velocity measurements from contrast slopes have clinical utility, the rapid growth of Doppler echocardiography suggests that velocity measurements provide valuable clinical information.

Other Clues From Contrast Echocardiograms

Cyclical opacification and clearing of the pulmonary artery after intravenous injection, viewed by suprasternal M-mode echocardiography, suggest patent ductus arteriosus.[23] The same phenomenon should be seen in aortopulmonary window, because the physiology is similar. The phenomenon is seen because during systole, contrast-containing blood is ejected from the right ventricle into the pulmonary artery, and in diastole the pulmonary artery receives contrast-free blood from the aorta through the ductus. Cyclical opacification of the IVC can be seen both in patients with tricuspid regurgitation (during the v wave) and in normal subjects (during the a wave), as mentioned. After peripheral intravenous injection in most normal subjects, cyclical variation can be seen in the intensity, direction, and velocity of contrast opacification across the tricuspid valve, in the right ventricular outflow tract, and across the pulmonary valve.

Contrast echocardiography is the only method that can follow the flow pattern of individual "particles" (in this case, microbubbles) through the heart. It is thus well suited to the analysis of vortexes, "streaming," and other abnormal flow patterns. Streaming refers to lack of complete mixing of blood in a chamber, so that blood from a certain origin proximal to that chamber preferentially flows to one or more specific distal destinations. This pattern is frequently seen in the right ventricle after intravenous injection.

Problems and Limitations

The most frustrating problem with contrast echocardiography is that it is not consistent and reproducible: An injection may produce excellent contrast and the following one with seemingly similar technique may yield little contrast. Furthermore, there is no guarantee that microbubbles in the circulation travel with exactly the same velocity as the surrounding blood stream. Their distribution across a vessel does not need to be uniform; they might preferentially gather in the area of lower velocity along the vessel wall or in the central stream of maximal velocity. Another possibility is that bubbles of different size have different behavior and that different populations preferentially seek the wall or the central stream. Although commercial microbubble contrast agents may alleviate some of these problems, it is unlikely to solve all of them. Awareness of methods that may increase the yield of contrast using "standard" agents,[39] or the addition of a small amount of medically pure carbon dioxide[40] can improve the yield of satisfactory contrast studies.

Intense contrast can "overload" the instrumentation in 1 of several distinct ways. Returning echoes can become too intense for normal processing by the instrument set for processing of echoes in the absence of contrast. This is especially true when Doppler echocardiography is being used. Ultrasound travels slower in air than in water and slower in the air-water medium of a microbubble suspension than in normal blood. Thus, spurious contrast echoes may be displayed at locations further away from the transducer after the sound beam has passed an area of intense contrast. If this phenomenon is not well understood, the echocardiographer runs the risk of falsely diagnosing a shunt by contrast echocardiography. Further, intense contrast can reflect so much of the ultrasonic beam energy that not enough is left to image more distal structures during the period of maximum contrast intensity, and "drop-out" results in the distal image. Finally, the gray scale capacity of both M-mode and 2-dimensional echocardiography allows a far smaller range of output than the range of ultrasonic signals returning to the transducer. Thus "video-display overload" occurs when a pixel is at its maximum brightness and the increased ultrasonic signal due to more intense contrast cannot be displayed as a further increase in videointensity.

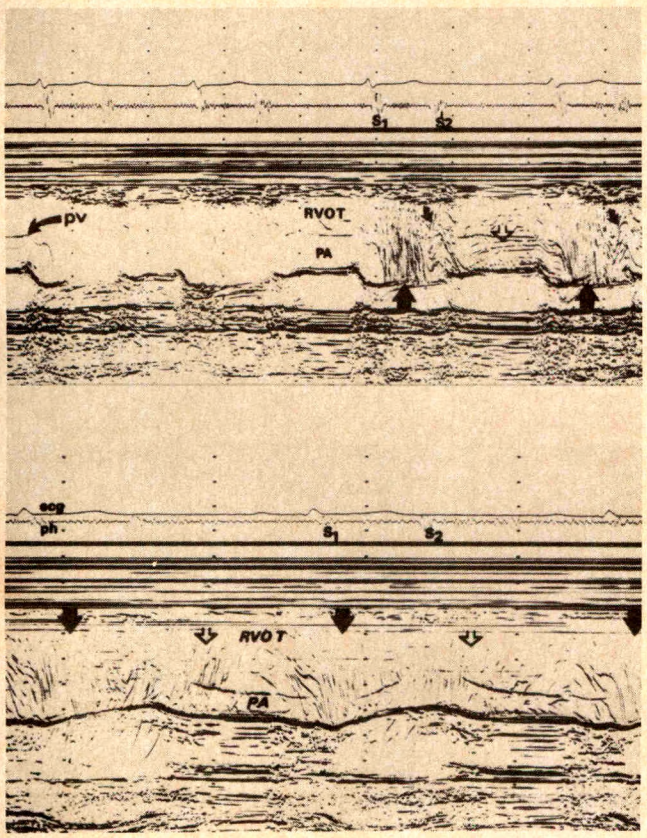

FIGURE 5. M-mode echocardiograms taken after peripheral intravenous dextrose injections with the echocardiographic transducer aimed in the right ventricular outflow tract (RVOT), pulmonary artery (PA) direction. **Upper panel,** in a normal patient, contrast material flows away from the transducer (anterograde) during systole (**heavy black arrows**). There is a short duration of retrograde flow toward the transducer coincident with S_2 (**short curved arrows**), and then no significant retrograde flow imaged during diastole (**open arrow**). **Lower panel,** in a patient with pulmonary insufficiency, contrast flows toward the transducer (that is, retrograde) throughout early diastole (**open arrows**).

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Left Atrial Abnormality As an Electrocardiographic Criterion For the Diagnosis of Left Ventricular Hypertrophy in the Presence of Right Bundle Branch Block

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Left atrial (LA) abnormality determined from precordial lead V_1 was assessed by 2 observers as a criterion of left ventricular (LV) hypertrophy in the presence of right bundle branch block (BBB) in 23 patients. The presence of LV hypertrophy was confirmed from a postmortem cardiac partition technique and defined at 2 levels of confidence: probable and definite hypertrophy. Observers reliably differentiated between the hypertrophied and normal-sized ventricle in the presence of right BBB by using LA abnormality as an electrocardiographic criterion. When defined as definite hypertrophy, observer 1 correctly identified LV hypertrophy in 78% of the cases and observer 2 in 67% of the cases. False-positive results were present in 21% of cases by observer 1 and 14% by observer 2. Comparable results were achieved when a definition of probable hypertrophy was used. Observer performance of recognition of LA abnormality in this study was satisfactory with 91% agreement between observers. Our results are comparable and in some instances superior to conventional criteria commonly recommended to diagnose LV hypertrophy on the electrocardiogram without right BBB.

Left atrial (LA) abnormality was carefully defined in the V_1 lead of the scalar electrocardiogram by Morris et al,[1] and was recognized as a marker of left ventricular (LV) hypertrophy in the development of electrocardiographic criteria.[2,3] Patients with a variety of cardiac disorders, including hypertension,[4] aortic stenosis,[5] and cardiomyopathies,[6] frequently exhibit the typical pattern of LA abnormality. In addition, Rios et al[7] found a high incidence of LA abnormality on electrocardiograms in patients with coronary heart disease and associated LV dysfunction. An elevated wedge pressure was observed in a majority of patients with LA abnormality studied by DiBianco et al,[8] indicating LV dysfunction, which is commonly associated with LV hypertrophy.

Left bundle branch block (BBB) on the electrocardiogram is associated with LV hypertrophy at autopsy in approximately 90% of cases.[9] In contrast, right BBB is not predictably associated with LV hypertrophy, and the usual electrocardiographic criteria recommended for LV hypertrophy may be unreliable in the presence of right BBB.[10,11] The criterion of LA abnormality compared with others may be used to advantage in the presence of right BBB. This autopsy study was designed to test the effectiveness of LA abnormality as an electrocardiographic criterion for detecting LV hypertrophy in patients with right BBB.

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Methods

From 1966 to 1979, 3,202 autopsies were performed at the Little Rock Veterans Administration Medical Center. Of these, 513 (16%) had a special cardiac examination using the methods of Schlesinger[12] and Reiner et al.[13] The first method provides information on the extent of coronary artery obstruction and the second allows division of the heart into specific left and right ventricular masses excluding epicardial fat, vessels, and valvular structures. Of these 513 patients, 26 had right BBB on the electrocardiograms as usually defined.[14] Three of these patients had atrial fibrillation and were excluded, leaving 23 with right BBB. These 23 form the basis of this report.

All 23 patients had satisfactory electrocardiograms performed with usual care and standardization as recommended[15,16] and were recorded on either a single-channel Burdick

model EK-5 or a Hewlett-Packard 1511B electrocardiograph machine. Postmortem coronary angiograms were scored as previously described.[17] On the basis of data from a control population using cardiac partition techniques, the degree of hypertrophy was defined as probable in those with a LV weight >177 g and as definite if LV weight was >200 g as previously described.[17] Right ventricular hypertrophy was considered present when the weight was >65 g.[18] Patient records were reviewed for clinical data. The definitions of coronary, hypertensive, and valvular heart disease and obstructive pulmonary disease were as previously reported.[17,18] Congestive heart failure was considered present if diagnosed by the examining physician based on the usual criteria.

The electrocardiographic criterion of LA abnormality as defined by Morris et al[1] was used. These consisted of a P-wave terminal force ≥0.04 second in duration and ≥1.0 mm in negative amplitude. To assess interobserver variability, 2 observers independently interpreted the electrocardiograms for LA abnormality.

The following conventional criteria recommended for the electrocardiographic diagnosis of LV hypertrophy in the presence of right BBB were evaluated by 1 observer (MM): (1) Lewis index: net positivity in lead I plus net negativity in lead III ≥17 mm[19]; (2) Sokolow index: S in lead V_1 + R in lead V_5 or V_6 >35 mm[20]; (3) R in aVL >7.5 mm[21]; (4) intrinsicoid deflection in V_5 or V_6 ≥0.05 second[22]; (5) left axis deviation >−30°[22]; and (6) tall R waves in lateral precordial leads[14] arbitrarily defined as >15 mm in V_5 or V_6 by this study.

Results

All patients were men, with an average age of 70 ± 12 years (mean ± standard deviation [SD]). There were 17 patients with coronary heart disease; 2 had associated hypertensive disease and 3 had associated chronic obstructive pulmonary disease. Of the remaining 6 patients, 1 had both hypertensive and chronic obstructive pulmonary disease, 2 chronic obstructive pulmonary disease, 1 valvular aortic stenosis, 1 cardiomyopathy, and 1 no organic heart disease. Thirty-nine percent of patients had heart failure. The right ventricular weight for the 23 patients was 58 ± 21 g (mean ± SD). The LV weight for the 23 patients was 195 ± 68 g (mean ± SD). Of the 23 patients, 12 had a LV weight >177 g, qualifying for our definition of possible LV hypertrophy, and in these 12 the LV weight was 247 ± 52 g (mean ± SD). Nine patients had a LV weight >200 g, qualifying as definite LV hypertrophy, and in these 9 the LV weight was 265 ± 46 g (mean ± SD). Right ventricular hypertrophy was present in 5 of 9 patients whose LV weight was >200 g, in none of 3 patients with an LV weight of 177 to 200 g, and in 1 of 11 of those with normal LV weight.

The average time from electrocardiography to the patient's death was 3.7 weeks (range 0 to 28). However, 86% of the electrocardiograms selected were within 8 weeks of death.

The results of analysis for the presence of LA abnormality in 23 patients with right BBB are presented in Table I. Observer 1 correctly diagnosed LV hypertrophy in 75 to 78% of the cases, with a false-positive diagnosis in 18 to 21%; observer 2 diagnosed LV hypertrophy in 58 to 67% of the cases with a false-positive diagnosis in 9 to 14%. These results varied according to the anatomic definition of hypertrophy. Therefore, the recognition of LA abnormality was helpful in separating the normal from the hypertrophied state in the presence of right BBB on the electrocardiogram.

TABLE I Left Atrial Abnormality on the Electrocardiogram in Patients With Right Bundle Branch Block As Related to Left Ventricular (LV) Hypertrophy Defined Pathologically

LV Size	Patients (n)	Observer 1 n	Observer 1 %	Observer 2 n	Observer 2 %
>177 g					
Hypertrophied	12	9	75	7	58
Normal	11	2	18	1	9
>200 g					
Hypertrophied	9	7	78	6	67
Normal	14	3	21	2	14

The performance of the observers can be expressed in the conventional terms of sensitivity and specificity. With LV hypertrophy defined as >177 g, observer 1 had a sensitivity of 75% and observer 2 of 58%; observer 1 had a specificity of 82% and observer 2 of 91%. With a definition of LV hypertrophy >200 g, observer 1 had a sensitivity of 78% and observer 2 of 67%; observer 1 had a specificity of 79% and observer 2 of 86%.

An evaluation of interobserver variability in recognizing the presence or absence of LA abnormality showed agreement in 21 of 23 cases (91%). The effect of this variability on results is presented in Table I.

The results of using conventional criteria for diagnosing LV hypertrophy (>177 g) in the presence of right BBB in our patients were as follows. No cases of LV hypertrophy were diagnosed with the Lewis index and there was 1 false-positive result. No cases were diagnosed with the Sokolow index. An R wave >7.5 mm in aVL was present in 1 of 12 cases, and an intrinsicoid deflection in V_5 or V_6 ≥ 0.05 second was present in 3 of 12 patients with LV hypertrophy. The latter criteria were false-positive in 1 patient. Left axis deviation >−30° was present in 13 patients. However, in only 6 patients was LV hypertrophy confirmed, leaving 7 instances of false-positive results. Tall R waves in V_5 or V_6 (arbitrarily defined as >15 mm) were seen in only 3 patients: 2 had LV hypertrophy and the other was a false-positive result.

Discussion

Our data show that recognition of LA abnormality on the electrocardiogram can be used to differentiate LV hypertrophy from the normal-size heart in the presence of right BBB. The sensitivity and specificity achieved in this study further substantiate this. LA abnormality as an electrocardiographic criterion was comparable or superior to conventional criteria commonly recommended for use in the diagnosis of LV hypertrophy in the absence of right BBB.[3]

The results of using recommended conventional electrocardiographic criteria for diagnosing LV hypertrophy in the presence of right BBB were unacceptable. These results have previously been substantiated by Booth et al,[22] who found that only 1 of 15 patients with

LV hypertrophy and none of 22 patients with combined hypertrophy could be diagnosed by the usual criteria in the presence of right BBB. However, some electrocardiographic textbooks still advocate the use of conventional criteria for the diagnosis of LV hypertrophy in the presence of right BBB.[14,19]

The definition of the magnitude of the LV mass constituting LV hypertrophy is arbitrary. Our own data suggest that a weight >177 g exceeds the normal range at a high probability.[17] However, a ventricular mass >200 g satisfies all criteria published for a hypertrophied left ventricle.[13,23] Only a modest difference in our results was noted regardless of the definition chosen. It is important to appreciate the reliability of the methods used in this study to determine specific ventricular mass in contrast to the unreliable indexes of wall thickness measurements.[24]

Our study was restricted to postmortem data of male patients. Studies of LA abnormality in living patients with right BBB and angiographic or echocardiographic determined LV mass would be of interest. Furthermore, we had no patients with mitral stenosis and congenital heart disease, so our results may not be applicable to them.

Observer variability was evaluated as part of this study and found to be acceptable, accounting for only a modest difference in results. Satisfactory observer recognition of LA abnormality was noted by Morris et al[1] and Forfang and Stoke.[25]

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Automatic Computer Processing of Digital 2-Dimensional Echocardiograms

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Quantitative studies of left ventricular function using 2-dimensional echocardiography have been limited because of a lack of computerized methods to automatically analyze the echocardiographic images. Previous computer efforts have been directed at digitizing the video output of the 2-D echocardiogram, but this digitizing method has significant limitations. A direct digitization method that produces improvement in signal-to-noise ratio and, subsequently, improved automatic detection of endocardial and epicardial borders, was developed. With definition of these edges, left ventricular global and regional analysis is possible frame by frame so that dynamic changes in cardiac function may be assessed throughout the cardiac cycle. Further technologic advances in 2-D echocardiographic acquisition and image processing should allow computer processing of 2-D echocardiographic data in real time.

Two-dimensional echocardiography (2-D echo) is particularly well suited to left ventricular (LV) functional analysis, in view of the many unique tomographic views that are available for study. However, assessment of LV function by 2-D echo remains largely qualitative because of intrinsic limitations of the ultrasound data, poor border definition in the stop frame video image, and the tedium of manual tracing of appropriate images.[1] Despite these limitations, operator-defined 2-D echo video images of tomographic LV sections have yielded important quantitative information concerning LV volume,[2,3] mass,[4] and function[4–6] with acceptable error.

Automatic computer processing of 2-D echo images would avoid the excessive time, labor, and subjectivity of manual tracing and would ultimately improve the reliability and validity of quantitative measures. Various techniques[7–10] for digitizing single frames of 2-D echo information are unsatisfactory because of the lengthy time required for digitizing a single frame of information, which eliminates any real-time capability, and the significant deterioration of the image as it is transferred through several optical systems into the computer memory.

Recently, Garcia et al[11] described an interface to a standard medical imaging computer from the video output of the 2-D echo unit or its videotape recorder. After space-time smoothing, they could automatically detect endocardial interfaces by standard threshold and second derivative methods. This report summarizes our recent work in computer acquisition and processing of 2-D echo images to quantify LV global and regional function. Our efforts initially involved acquisition and processing of 2-D echo video data,[12] but more recently we developed a method of direct-line data acquisition for 2-D echo.[13] Using the directly acquired data, we have used a number of edge detection algorithms to determine most anatomically appropriate borders. In parallel with this, we have developed a program for LV functional analysis for quantitative studies.

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Methods

Digitization and processing of 2-D echo video data: Our initial attempts at computer processing of 2-D echo images were performed using a medical imaging system coupled to the video output of our 2-D echo unit.[12] The parasternal LV short axis at the midpapillary muscle level was digitized into

FIGURE 1. A parasternal, left ventricular, short-axis, video output–acquired 2-dimensional echocardiographic image after processing with superimposition of endocardial and epicardial edges.

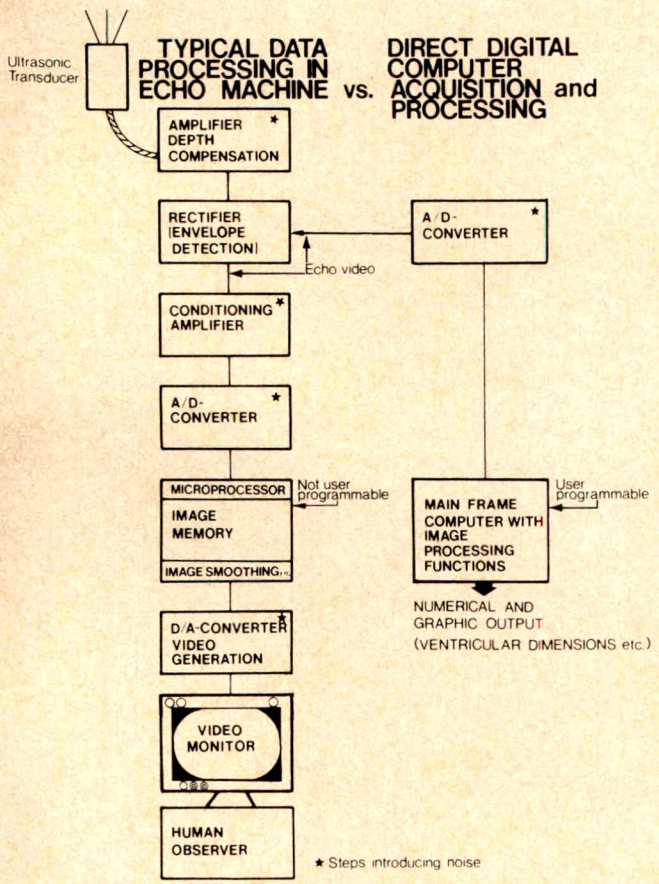

FIGURE 2. The processing steps in a commercial sector scanner and our method of direct digitization of the envelope-detected signal. Several steps of noise introduction are avoided by the direct digitization.

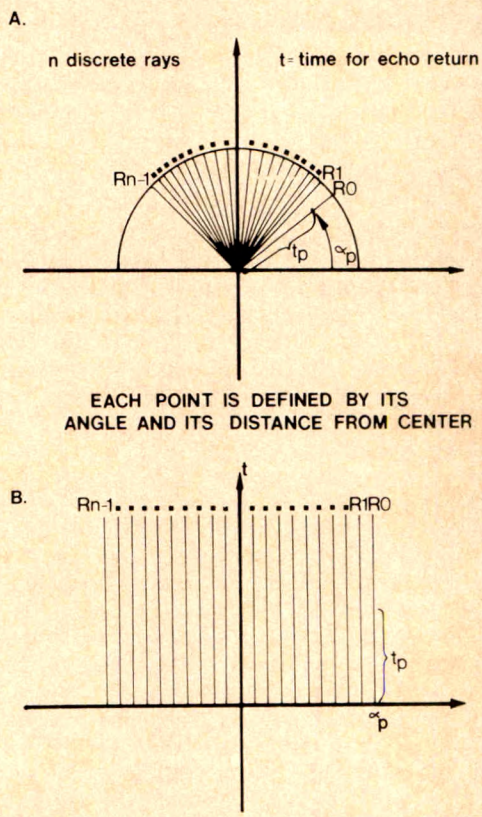

FIGURE 3. The mapping of the sector B-mode fan format (**A**) into a rectangular matrix (**B**).

a 64 × 64 array at 30 frames/sec and stored on magnetic tape for further processing. A total of 20 cardiac cycles were collected, electrocardiogram gated on the R wave. These digitized data were transferred by way of magnetic tape to the University of Michigan Computer and Image Processing Research Network.

Our processing began with the spatial averaging of time-aligned frames to produce a composite cardiac cycle of 29 images. Spatial smoothing further eliminated noise. An axially applied gradient method using 12 radial chords spaced 30° apart and originating at the center of the LV cavity was used to identify endocardial and epicardial boundaries. This approach produced short-axis LV images that were anatomically appropriate (Fig. 1).

Real-time line-mode data acquisition: Wells and Woodcock[14] distinguished between 2 approaches to echo

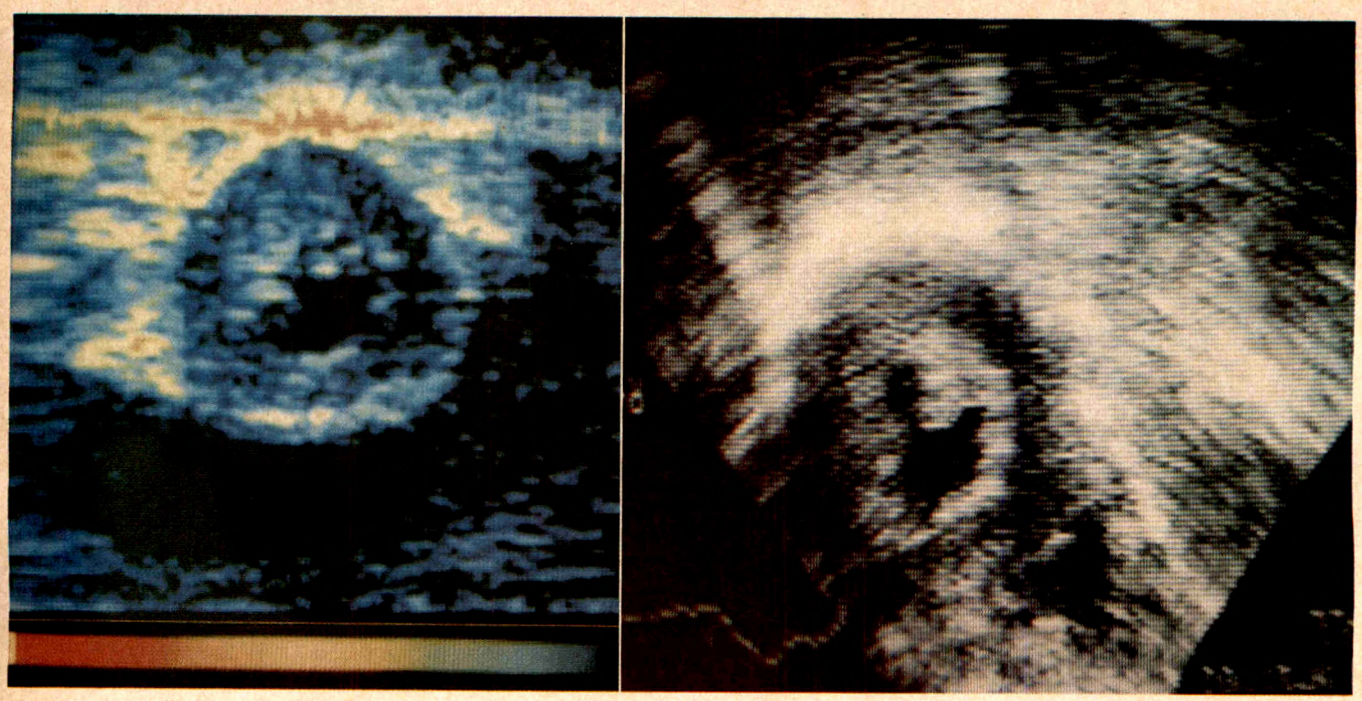

FIGURE 4. Left panel, a parasternal left ventricular end-systolic 2-dimensional echocardiographic image taken directly from the video display. **Right,** the same image acquired using direct-line mode digitization. The shape of the left ventricle is somewhat distorted because of the rectangular matrix format, but endocardial and epicardial definition is improved.

signal digitization. They termed methods which digitized the usual visual output of the echo unit "digitization of analog recordings" and termed methods in which the radio frequency (RF) signal or the envelope-detected signal was directly fed to an A/D converter "direct digitization." The term "line-mode data" has been applied to data digitized along the ultrasonic line of sight with positional information.[15]

To further improve the data at its source, we implemented direct-line digitization of our 2-D echo data (Fig. 2). We modified our computer's video A/D converter for horizontal and vertical synchronization by external digital signals. The analog section was rebuilt to adapt to the post-time-gain compensation envelope-detected RF signal from the echo machine. The pixel clock that determines the sampling rate along a line was set to 2 MHz.

From the digital-beam steering logic in the phased-array echo machine, 2 synchronization signals were derived: 1 for the firing of the center transducer element and 1 at the beginning of the first fan beam. The envelope-detected signal was amplified and transmitted directly to the A/D converter through a coaxial cable. Synchronization signals were sent through line drivers and coaxial cable to the synchronization input of the A/D converter. The process was controlled by an assembly language program with the same features as the television image digitization control programs, except that the image size was flexible to 128 × 256 pixels. R-wave triggering was used to synchronize the digitization.

The B-mode signal fan rays were thus mapped into a rectangular matrix (Fig. 3). Since 128 fan lines were produced by the echo machine and all of them were digitized, there was no data loss within a single fan frame (Fig. 4). However, the digital transfer rate of the whole frame to magnetic disk was too slow to begin acquisition of the next fan frame. Thus, only every other fan frame was digitized. The row index of a matrix element was the ray number in which a specific resolution element was sampled; the column index is the time of sampling measured from the center element transmit pulse. Only straight lines through the center of the source data coordinate system map into straight lines in the rectangular data matrix. An M-mode reconstruction from the columns of the rectangular matrix represents M-mode lines along the fan lines; an M-mode reconstruction along any other line is possible using the mapping function. Frame-to-frame and cycle-to-cycle averaging techniques for noise reduction are implemented easily in the software of this system using the programming language.

Digital processing of line-mode data: In our initial work, the images at the same location in the cardiac cycle were temporally averaged to produce a representative cardiac cycle. The images were then spatially smoothed and a 1-dimensional axial-gradient operation was performed. Regional wall measurements were digitally computed from the sequence of composite images to assess dynamic changes in wall thickness and chamber size throughout the entire cardiac cycle. Each frame was analyzed as a separate image and the adjacent frame redundancy was not exploited after the average cycle images were spatially registered.

We have extended our previous work of boundary detection and estimation of LV wall thickness and volume by treating the images as a problem in time-varying image analysis.[16] As the heart contracts, it is rotating, translating, and deforming. The problem of locating the endocardial boundary is treated as a problem of tracking a boundary of an object as it moves through a scene.[17]

The edge detector we use is a modified version of the axial gradient method previously described.[12] The algorithm begins by finding the center coordinates of the heart chamber in each frame. The images in our initial studies are interpolated to sector format from the line-mode format. The center is found by starting at any point within the chamber and locally

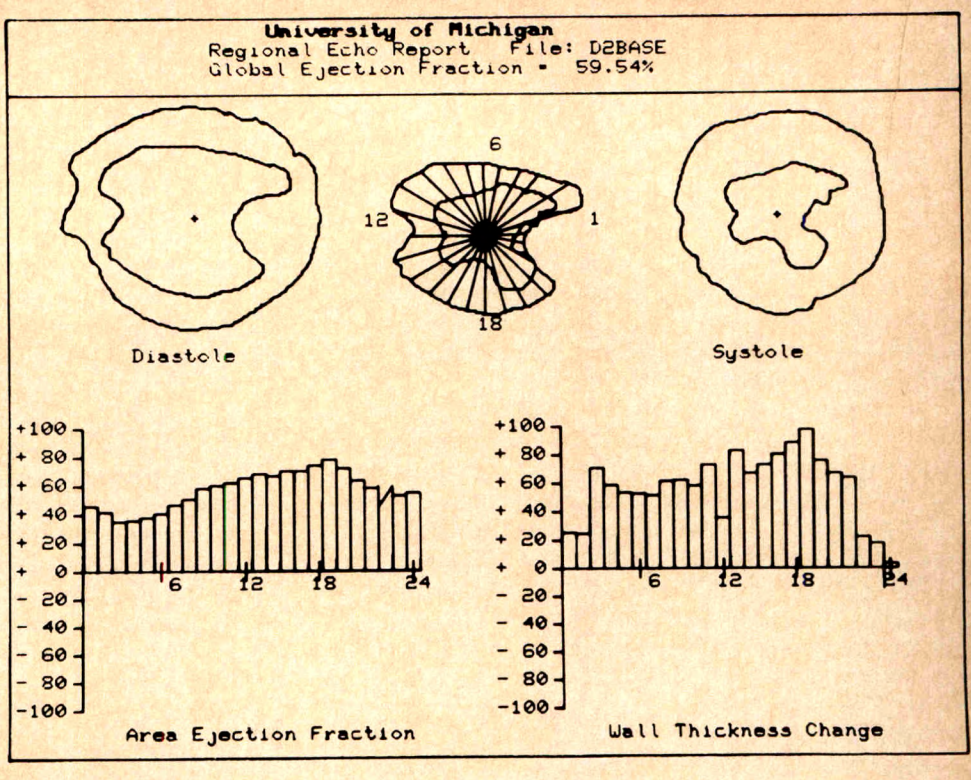

FIGURE 5. Regional analysis program used for quantitative 2-D echo studies. See text for details.

searching with a thresholding algorithm to find the endocardial boundaries. The locations are then averaged to obtain the center of the chamber. If the thresholding algorithm cannot find the endocardium in a region due to each dropout, that local region is not used to estimate the center of the chamber. This method is a fast and accurate technique for finding the center of the chamber, because the endocardial borders are as easily found by local thresholding. Once the center coordinates of each frame are found, the algorithm starts from the center point and moves along rays separated by 30°, computing the first derivative of the gray levels along the ray. The endocardium is assumed to be located where the derivative changes sign. The endocardium is found by starting at a location at the edge of the image. The derivative is computed as the ray is searched inward; when the derivative changes sign in this direction, the epicardial border is located. The edge points are then connected to form closed contours using linear interpolation. To minimize artifacts in the boundaries using this algorithm, we are investigating the use of a connectivity test to determine if the boundary has sharp changes. This is manifested by a small radius of curvature in the boundary. If the connectivity test fails in that a small radius of curvature is found in a boundary, we use this as a constraint in the algorithm to force the detector to find edges that do not have sharp boundaries. Our results using the connectivity test are only preliminary but are very promising.[18]

The edge detector described above is a static edge detector in that it operates on single frames in the cardiac cycle. We are exploiting the temporal redundancy inherent in the data. While there are various approaches to this problem, we are considering a simple method: difference pictures. Difference pictures are created by obtaining the frame difference between the current frame in the cardiac cycle and the previous frame. After thresholding, this difference picture then indicates regions in the image where the heart has moved. The edge detector algorithm described above is modified so that only regions in which the heart wall has moved are used in searching for the edges in that frame. This aids in finding the edges because the difference pictures indicate where along the rays the edges in the current frame are located. This technique can also be used to limit how much the edges are allowed to change from frame to frame.

Using this approach, we found that cycle averaging and spatial smoothing may not be necessary with the directly digitized line-mode data. In fact, the edges found for each image in a cycle have fewer artifacts and tend to preserve edge connectivity throughout the cycle.

Quantitative analysis of the left ventricular image: In parallel with our efforts at 2-D echo direct line-mode digital acquisition, image processing, and edge detection, we have developed a program to analyze regional LV function. This analysis may be applied to any LV short-axis projection and the derived data in combination with long-axis data may be used to estimate global LV function and mass using well-described algorithms such as Simpson's rule.

In this analysis, the endocardial and epicardial borders of the LV at end-diastole and end-systole are manually entered into the computer using a Tektronix digitizing tablet. A menu displayed on the image device guides and prompts the operator for data input. The data input consists of epicardial and endocardial borders, external alignment points for the systolic and diastolic images, and 5 cm magnification calibration points. Once all the data have been entered, the program calculates the center of mass of the diastolic endocardial border, the rotation angle, and translation coordinates for alignment of the systolic borders over the diastolic borders. These aligned borders are then stored in a protected disk file for archival and research use. Calculations are performed using the center of mass of the end-diastolic endocardial border as the reference point. The continuous borders are separated into 24 segments, each of 15°, for calculation of regional ejection fraction, regional wall area, and regional wall

thickness (Fig. 5). There is a graphic display of proportional change, diastole to systole, along with the segmented systolic and diastolic borders.

Discussion

The interpretation of LV function by 2-D echo largely remains a descriptive technique requiring expert observers. Quantitative analysis has involved manual delineation of endocardial and epicardial boundaries of end-diastolic and end-systolic frames by trained operators. Other frames of the cardiac cycle are generally not analyzed because of the time and labor involved. The ability to further automatically process these 2-D echo images should improve our ability to quantitate 2-D echo data, provide a more objective approach to interpretation, and improve interobserver variability. The major limiting factor to the development of computer processing of 2-D echo has been the long acquisition times required to digitize a single frame of data. However, digital interfaces specific to ultrasound make it possible to acquire digital 2-D echo data in real time. Owing to the inherent complex interaction of ultrasound in tissues and the several steps of processing that occur within the commercial 2-D echo unit, these digitized data are noisy.

In our initial approach to acquisition of 2-D echo data, the video output of the unit[12] was digitized. This method has several flaws. First, the resampling process required to form a video image from the line-mode data tends to produce undersampling of data in the near field and oversampling in the far field. Second, the ultrasound frame generation may not match the video frame rate. Third, the scan converter within the echo unit maps the information into a range of gray values with a dynamic range matched to the human visual system; however, the usable dynamic range of the data is significantly greater. Fourth, the averaging technique for speckle reduction is usually not under user control. Fifth, the video image data depends on the processing performed by the echo technician, who varies the control settings on the echo unit to achieve an image that looks best to the human observer; however, this image may not necessarily be optimal for computer processing. For these reasons, we approach the digital acquisition of 2-D echo data through direct line-mode digitization.[13] With this approach, RF envelope-detected data are digitized before data transfer to the digital scan converter. This avoids the introduction of noise at several levels of data conversion and provides improved signal-to-noise ratios.

Robinson and Williams[15] indicated that this method is superior to other methods of digitization for 2-D echo processing. In addition, this line-mode digitization method has several advantages over conventional video image digitization. First, the ultrasound frame generation rate is equal to the A/D frame conversion rate; this condition is not necessarily fulfilled by video image digitization. Second, the envelope-detected signal is independent of all control settings on the echo unit except for gain control. Third, the dynamic range of the 8-bit line-mode data significantly exceeds that of the typical 4- to 6-bit output of the digital scan converter used for video data acquisition. For these reasons, we believe that line-mode data digitization is presently the preferred method of ultrasound data acquisition for computer processing.

Image processing and algorithm development have been undertaken on our computer system. After applying Laplacian, Sobel, trapezoidal, and high-pass filtering edge detection routines, our approach of axial gradient edge detection appears to be the simplest and most accurate for providing anatomically appropriate endocardial and epicardial definition. With the line-mode digitization, temporal or spatial smoothing or both may produce artifacts in our automatically derived edges.[16] These smoothing techniques may be better suited to 2-D echo video data, for which they provide some improvement in signal-to-noise ratios. Further algorithm development, testing, and validation are required before clinical application of these techniques is attempted. Although our axial gradient technique is used, we believe that edge detection would be improved by using a time-varying image analysis approach[17,18] in which edge redundancy in frame-by-frame analysis would be used to provide further improvement in edge tracking. This form of dynamic scene analysis has been used in other imaging problems with success.[19,20]

Assuming that appropriate edges can be found and validated, a quantitative approach to global and regional analysis would then be necessary. Several attempts at LV function quantitation have been undertaken with manually defined edges, with variable success.[2–6] Although good correlations with standard measurements have been achieved, there remains 10 to 20% variability in the measurement of LV volumes and mass. This variability derives from tomographic trajectory, poor endocardial definition, observer error, and, of course, additional variability of the gold standard method.[21] For instance, in contrast LV angiography, the contrast material produces volume loading and a negative inotropic effect,[22] contributing to discrepancies with other imaging techniques. Automatic methods of edge detection and quantitation for 2-D echo should reduce interobserver variability but will not influence these other factors, which require different solutions. A major impact of automatic quantitated processing will be the time saved in analysis and the ability to measure dynamic information contained within the entire cardiac cycle.

The quantitative analysis of regional function that we have developed is similar to approaches previously described.[6,11] However, controversy continues regarding the use of coordinate systems and correction of 3-D movement.[23] This problem is best illustrated by the variability of regional analysis, which depends on whether a fixed or floating center of mass is used.[6] Although axial coordinates have been traditionally used with most cardiac imaging modalities, the unique tomographic information provided by 2-D echocardiography permits an approach to shape descriptors using Fourier shape analysis or mean tensor analysis.[24] These forms of analysis may circumvent the problem introduced with a coordinate, axial approach to quantitative regional LV function.

We anticipate further improvements in digital data acquisition, image processing, development of edge

detection algorithms, and methods of quantitation of 2-D echo images. These improvements should then provide a basis for meaningful 3-D reconstruction[25] of 2-D echo images.

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Early Degradation of Collagen After Acute Myocardial Infarction in the Rat

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After acute myocardial infarction (MI), proteolysis of necrotic myocardium is mediated by infiltrating inflammatory cells at the infarct margins. Collagen forms a structural fibroskeleton in healthy myocardium, and after MI this collagen may continue to provide significant tensile strength to the necrotic muscle wall. To determine whether collagen is also degraded (which might decrease infarct wall strength) and, if so, whether inflammatory cell proteases are implicated, hydroxyproline was measured from infarct zone and normal zone tissue from 24-hour infarcts produced in control rats and in rats made leukopenic (white blood cell count $<300/mm^3$) by prior whole-body irradiation. Hydroxyproline was measured after precipitation of tissue homogenates with trichloroacetic acid to separate partially degraded collagen from larger collagen molecules that might retain structural importance. At 24 hours, there was significant (25%) collagen degradation in the infarct zone ($p < 0.01$) in control rats but not in leukopenic rats. Tissue cell counts revealed a paucity of inflammatory cells in the infarct margins in leukopenic rats. Electron microscopic studies revealed greater preservation of collagen in the 24-hour-old infarcts of irradiated leukopenic rats compared with those of control rats. These results suggest that at 24 hours after experimental MI in the rat, there is significant collagen degradation mediated by inflammatory cell proteases.

Collagen forms a structural network for the attachment and alignment of heart muscle cells.[1] The arrangement of this network probably prevents slippage of myocytes during systole, tends to maintain the patency of capillary lumina during systole, and provides tensile strength to the heart muscle wall. After myocardial infarction (MI), when heart muscle cell death and degeneration occur, this collagen fibroskeleton may be important in maintaining the integrity of the ventricular wall until new collagen deposition and scar formation begin. We have demonstrated that proteolysis of necrotic myocardium significantly increases by 18 to 24 hours after experimental MI in the rat,[2] concomitant with an influx of inflammatory cells at the infarct margins. It is possible that inflammatory cell proteases jeopardize existing collagen soon after MI, potentially leading to wall thinning or rupture before new collagen formation. This study assesses the effect of inflammatory cell proteases on left ventricular myocardial collagen after experimental MI.

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Methods

Experimental myocardial infarction: Sprague-Dawley male rats that weighed 250 g and had been maintained on rat chow (Purina) and water ad libitum were anesthetized with ether. A left thoracotomy was performed, and the heart was manually expressed from the chest cavity. A 4-0 silk suture ligature was placed around the left coronary artery at the level of the tip of the left atrial appendage.[3] The heart was rapidly repositioned in the chest, the wound closed with a previously placed purse-string suture, and the rat resuscitated. This model results in transmural infarcts of 30 to 50% of the left ventricle, with sparing of the interventricular septum. An operative mortality of approximately 25% was encountered and deaths after 6 hours postinfarction were uncommon. The rats were killed at 24 or 72 hours for collagen content determination and histologic studies. Unoperated control rats were also killed for comparison. Another group of rats underwent whole-body irradiation with 800 rad from a cesium-137 source (Gammacell 40, Atomic Energy of Canada). Two days after irradiation, significant leukopenia as determined by hemocytometer counting[4] developed in all rats (Table I). At this time, the rats underwent coronary artery ligation as described above. There was no excess mortality in this group compared with that of the nonirradiated controls. By 24 hours after in-

TABLE I White Blood Cell Count—Control and Irradiated Rats

	Unoperated	24 Hours After Myocardial Infarction
Controls	13,275 ± 811 n = 13	14,167 ± 651 n = 9
Irradiated	3,016 ± 258* n = 29	302 ± 56* n = 24

White blood cell counts expressed as cells/ml, mean ± standard error. Counts on unoperated, irradiated rats were measured at 48 hours after 800 rads of whole-body irradiation (before coronary artery ligation) and at 24 hours after ligation (72 hours after irradiation).
* $p < 0.001$ versus respective control.

farction (3 days after irradiation), profound leukopenia was found in all rats (Table I). The rats in this group were then killed for myocardial collagen content determination and histologic study. Because of an increasing mortality rate >3 days after irradiation, collagen measurements and histologic studies were not performed 72 hours after infarction in leukopenic rats.

Collagen measurements: Collagen content was assessed by measuring hydroxyproline, which comprises a relatively constant 14% of collagen molecules and is found in few other tissue proteins in significant quantity.[5] After the rats were killed by a blow to the head, the heart was rapidly removed and rinsed in normal saline solution. The infarct was excised from the remaining myocardium and transmural samples of the infarct zone, as well as normal tissue from the interventricular septum (normal zone), were separately dried in an oven at 60°C for 1 hour. The tissue, ranging in dry weight from 25 to 40 mg, was homogenized in 2.0 ml of water. The homogenate from each sample was precipitated in 0.5 ml cold 50% trichloracetic acid (TCA, final concentration 10%) in order to separate large protein molecules from partially or completely degraded peptides (less than approximately 12,000 molecular weight), which would remain in the supernatant.[6] After centrifugation at 5,000 rpm for 20 minutes at 5°C, the supernatant was removed and the precipitate resuspended in 2.0 ml of water. Then, 0.25 ml of 1 *M* sodium hydroxide and 2.0 ml concentrated hydrochloric acid (final concentration approximately 6 *M*) were added to each sample. After thorough mixing with a vortex mixer, the samples were placed in Teflon-capped tubes and heated in an oven at 110°C for 12 hours. Hydroxyproline assay by the colorimetric method of Prockop and Udenfriend[5] was performed after completing the acid hydrolysis. To ensure that TCA did not alter hydroxyproline during acid hydrolysis, duplicate samples of 0.5 m*M* hydroxyproline (H6002, Sigma) and three 1:1 serial dilutions (0.25 m*M*, 0.125 m*M*, 0.063 m*M*) were assayed in an identical manner as the rat myocardial tissue. The assay results were plotted against the known standard concentrations, with excellent correlation ($r = 0.95$).

Microscopic examination: Another group of control and irradiated rats underwent coronary artery ligation and were killed at 24 hours. The hearts were rapidly excised and placed in normal saline solution until contraction ceased, then fixed in 10% acetate-buffered formalin solution or 3% glutaraldehyde. Formalin-fixed hearts were sliced from base to apex in a plane parallel to the atrioventricular groove beginning at the level of the suture ligation, resulting in 4 transverse slices each 2 to 2.5 mm thick. After embedding in paraffin, 6-μm-thick histologic sections were obtained from the middle of each slice and stained with hematoxylin-eosin. The histologic sections of all 4 slices from each heart were projected onto a screen at a 10-fold magnification, and the areas of normal and infarcted myocardium measured by planimetry. Infarct size was determined by averaging the percent infarcted area in each of the 4 slices. Kodachrome slides were taken at 400 × magnification of 10 representative areas of infarct margins from 5 control and 5 irradiated rats at 24 hours after infarction. The slides were projected on a grid-arrayed screen of known dimensions. Polymorphonuclear leukocytes (PMNs) were counted by 2 observers without knowledge of the identity of the slides. The average cell count of 10 slides for each rat was expressed as the number of PMNs/mm^2 of tissue section.

For electron microscopic study, the hearts were cut transversely into 5 slices, which were placed in 3% glutaraldehyde in 0.1 *M* phosphate buffer, pH 7.2. From the third of these slices, small tissue samples were obtained from the infarct margins, the infarct core, and normal septal myocardium. These samples were washed with several changes of 5% sucrose in 0.1 *M* phosphate buffer, pH 7.2; postfixed with 1% OsO_4 in Millonig's phosphate buffer, pH 7.2; dehydrated with a graded series of ethanols and propylene oxide; and embedded in Maraglas using flat embedding molds to preserve the orientation of the endocardium. One-thick sections of Maraglass-embedded tissues were stained with alkaline toluidine blue and examined with a light microscope in order to select areas for ultrathin sectioning. Ultrathin sections were stained with ethanolic uranyl acetate and lead citrate and examined with a JEOL 100B electron microscope at an accelerating voltage of 80 kV.

Statistical analysis: All data were analyzed using unpaired two-tailed Student's *t* test. A p value <0.05 was considered significant. Data are expressed as mean ± standard error of the mean.

Results

Measurement of TCA-precipitable hydroxyproline in unoperated rats revealed no significant difference between the collagen content of left ventricular free wall (9.2 ± 0.5 nmol/mg dry weight) and septum (10.6 ± 0.8

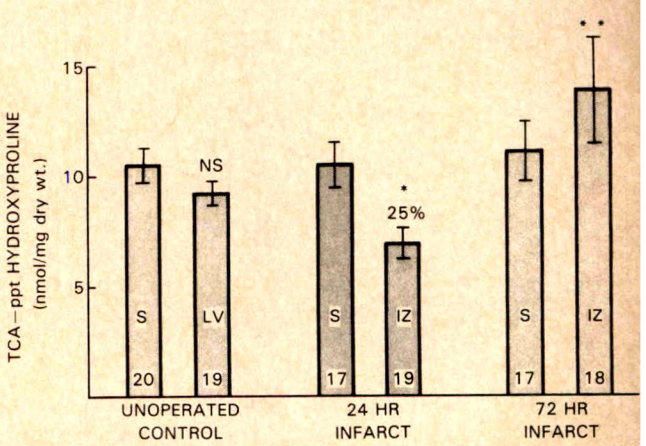

FIGURE 1. Hydroxyproline content from unoperated rats and control rats at 24 and 72 hours after coronary artery ligation. There was no significant difference between septum (S) and left ventricular free wall (LV) in unoperated rats. Note the significant decline in hydroxyproline content in infarct zone (IZ) tissue 24 hours after infarction compared with unoperated control left ventricular tissue. By 72 hours, there is a significant increase in hydroxyproline content of the infarct zone compared with 24 hours postinfarction IZ tissue. Results are expressed as mean ± standard error. Number at the bottom of each bar indicates the number of rats studied. * $p < 0.01$ versus unoperated control LV tissue. ** $p < 0.001$ versus 24-hour IZ. TCA = trichloroacetic acid.

nmol/mg dry weight; Fig. 1), in agreement with previously published measurements in rat myocardium.[7] There was no significant difference between the collagen content of normal zone tissue from the ventricular septum (10.6 ± 1.1 nmol/mg dry weight) of rats of 24 hours after coronary artery ligation when compared with septal tissue from unoperated control animals. However, there was 25% reduction of TCA-precipitable collagen in the infarct zone (6.9 ± 0.7 nmol/mg dry weight, $p < 0.01$) at 24 hours after infarction compared with left ventricular tissue of unoperated rats. Conversely, rats made leukopenic by whole body irradiation before infarction had insignificant collagen degradation (9.9 ± 1.2 nmol/dry weight, Fig. 2) at 24 hours after MI (3 days after irradiation) in infarct zone tissue compared with left ventricular tissue of unoperated control animals 3 days after irradiation (11.0 ± 0.8 nmol/mg dry weight).

Nonirradiated rats had a greater amount of collagen in the ischemic zone at 72 hours (13.9 ± 2.5 nmol/mg dry weight than at 24 hours (6.9 ± 0.7 nmol/mg dry weight, $p < 0.001$) after infarction (Fig. 1). Collagen content in septal tissue was not significantly different at 24 hours (10.6 ± 1.1 nmol/mg dry weight) and 72 hours after MI (11.2 ± 1.3 nmol/mg dry weight).

Histologic observations: As determined by planimetry, the sizes of 24-hour-old infarcts were identical in control (43.5 ± 2.8% of left ventricle, n = 17) and irradiated animals (43.5 ± 3.4% of left ventricle, n = 13) at 24 hours after MI. Light microscopic comparison of transverse ventricular sections of normal and irradiated rats 24 hours after acute MI revealed a marked diminution of the acute inflammatory response in the irradiated animals (Fig. 3). The distribution of inflammatory cells at the margin of infarcted and viable myocardium was similar in both animal groups. Correspondingly, myocyte damage and nuclear debris were most evident at the infarct margins, although they were much more extensive in the control rats.

Tissue cell counts: Cell counts from the border zone of control rats at 24 hours after infarction demonstrated an average of 416 ± 43 PMNs/mm^2 of tissue section, with prevalent "nuclear dust" representing leukocytes in various stages of degranulation and degeneration. Conversely, irradiated rats demonstrated a paucity of PMNs: 75 ± 11 PMNs/mm^2 ($p < 0.001$ versus control animals).

Electron microscopic observations: Electron microscopic examination of infarct core tissue from the control and irradiated rats revealed the known ultrastructural changes of ischemic necrosis in the myocytes.[8] An infiltrate of polymorphonuclear leukocytes was present in the border zones of infarcts from control hearts (Fig. 4). In this group of hearts, the connective tissue in the border zone showed fragmentation of collagen fibrils, the damaged ends of which seemed to be disrupted into fine granules. These changes were considered indicative of degradation of collagen fibrils because of their striking similarity to those that occur in damaged collagen in other conditions (for review see Ferrans et al[9]). They were less pronounced in the infarct core and were not present in the normal zone (septum).

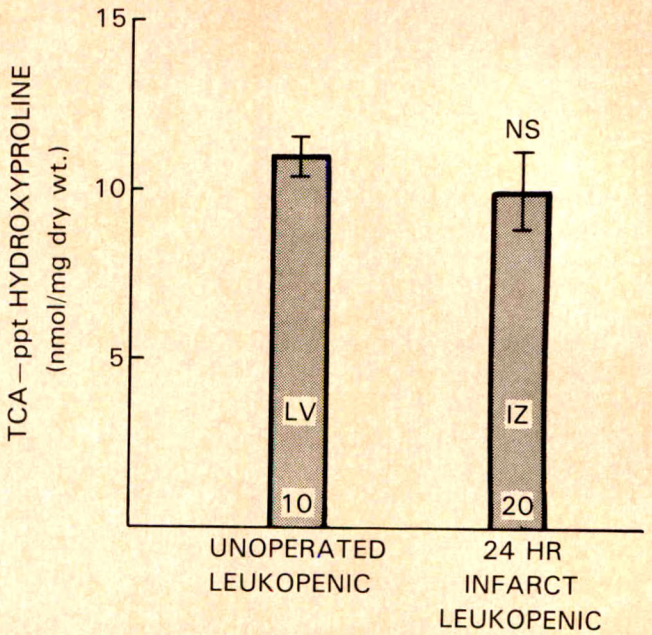

FIGURE 2. Hydroxyproline content from unoperated rats and rats at 24 hours after infarction. Both groups were 72 hours postirradiation (800 rad whole body). The hydroxyproline decrease in the infarct zones of control rats (Fig. 1) is not seen in irradiated leukopenic rats. Results are expressed as mean ± standard error. IZ = ischemic zone; LV = left ventricle; NS = not significant compared with unoperated leukopenic left ventricle; TCA = trichloracetic acid; numbers at the bottom of each bar indicate number of rats studied.

The alterations just described involved the small bundles of collagen fibrils coursing between individual myocytes as well as larger collagenous septa enveloping groups of myocytes. Tissue from the 24-hour irradiated leukopenic rats (Fig. 5) showed considerably fewer polymorphonuclear leukocytes and significantly greater preservation of collagen in the border zone and the infarct core.

Discussion

Although the association of extracellular connective tissue with myocytes has been appreciated for many years, the structural arrangement of the elaborate fibroskeleton of the heart has been demonstrated only recently. Using transmission and scanning electron microscopy, Caulfield and Borg[1] demonstrated that the network of collagen fibers in both animal and human hearts has 3 basic components. First, bundles of collagen fibers (measuring 120 to 150 nm in rodent hearts, somewhat larger in human hearts) extend between adjacent myocytes, inserting near the Z bands and the points of origin of the transverse tubular system. These intermyocyte connections appear curved in hearts arrested in systole and straightened in hearts arrested in diastole. It has been suggested that such connections align and mechanically couple myocytes, preventing slippage during systole. Additionally, these collagenous connections become thickened (250 to 300 nm in humans) in hypertrophied hearts. The second component of the collagen fibroskeleton consists of connections between myocytes and capillaries. Such connections

allow for capillary patency during high intraventricular systolic pressures and possibly explain the observation of systolic intramyocardial blood flow.[10] Most important from the standpoint of myocardial stiffness[11] may be the third component, a web network of collagen fibers that envelop groups of myocytes and have loose collagen connections between these groups, allowing slippage to occur. This weave configuration of collagen may have viscoelastic properties that contribute to left ventricular compliance.[12] Other connective tissue components, such as basal laminae, elastin, microfibrils, fibronectin, and proteoglycans also are undoubtedly important in the linkage of collagen to myocytes and capillaries.

Our experiments demonstrate significant degradation of collagen in rat MI by 24 hours after coronary artery ligation. The design of these experiments may have allowed for an underestimation of the degree of collagen degradation. Because TCA precipitates large proteins of greater than approximately 12,000 molecular weight, large, partially hydrolyzed collagen fragments that would have little or no structural importance could have been measured along with intact collagen molecules. Certainly, smaller collagen polypeptides and component amino acids with no structural significance could be separated by this precipitation technique. This collagen proteolysis was associated histologically with an influx of inflammatory cells, especially polymorphonuclear leukocytes, at the infarct margins. The fact that leukopenic rats demonstrated less degradation of collagen, as shown by biochemical measurements and ultrastructural observations, suggests that inflammatory cell proteases are responsible for collagen proteolysis. Polymorphonuclear leukocytes and marcrophages are known to contain several potent proteolytic enzymes, including collagenase.[13] Histologically, the margins of 24-hour infarcts contain polymorphonuclear leukocytes in various stages of degeneration and degranulation, changes indicative of the release of proteolytic enzymes. Collagenase is crucial for the initial degradation of collagen, although after initial cleavage by collagenase, other proteolytic enzymes contained within PMNs can further degrade collagen.[14]

During the early hours after MI, when lysis of necrotic myocytes is occurring, the collagen fibroskeleton described above would not be immediately affected by ischemia and may provide significant tensile strength

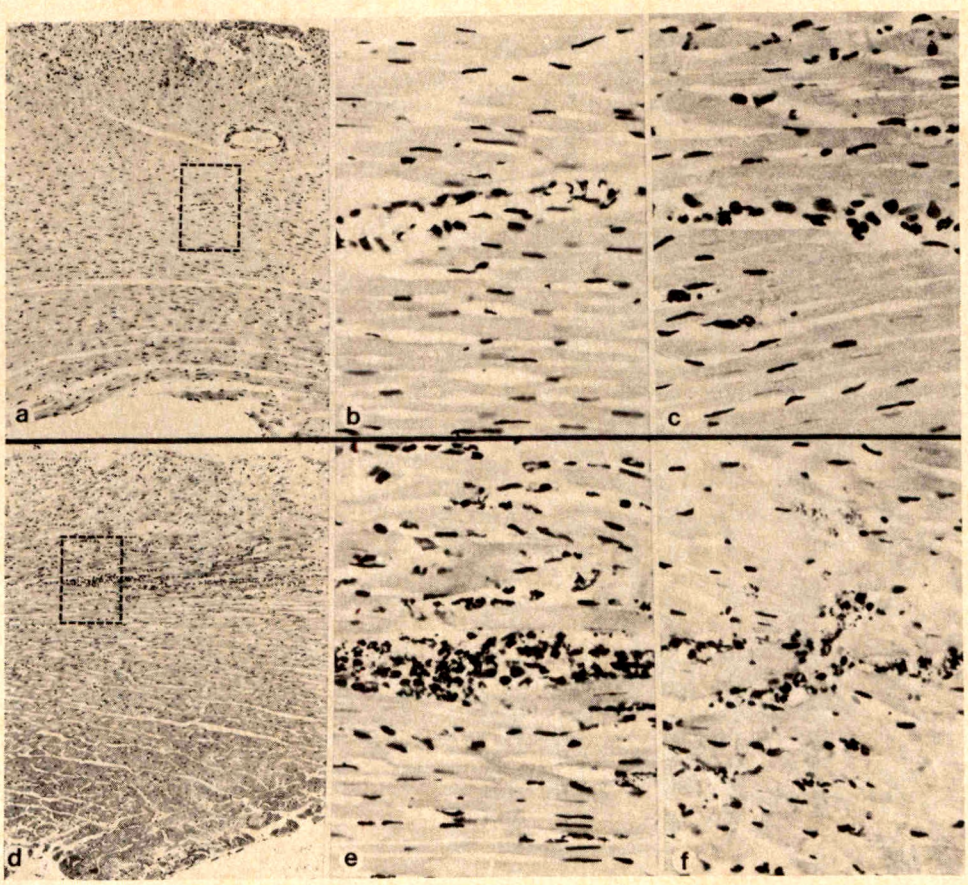

FIGURE 3. Photomicrographs of the anterior left ventricular free wall at the site of acute myocardial infarct 1 day after coronary artery ligation in irradiated (**a, b, c**) and control (**d, e, f**) rats. **a,** rare inflammatory cells are seen in the central area of the infarct in irradiated animals. **b,** higher power of the demarcated area in **a,** showing the paucity of perivascular or interstitial inflammatory cells. **c,** margins of the infarct have a few more inflammatory cells, including polymorphonuclear leukocytes and monocytes. **d,** a more pronounced inflammatory cell infiltrate is evident in the control rats. **e,** higher power of the demarcated area in **d** showing numerous inflammatory cells and early myocyte degeneration and necrosis. **f,** margins of the infarct also have numerous inflammatory cells, mostly fragmented leukocytes. Myocyte necrosis is more extensive and advanced. Hematoxylin-eosin stains; magnifications × 100 (a, d), × 550 (b, c, e, f,), reduced 48%.

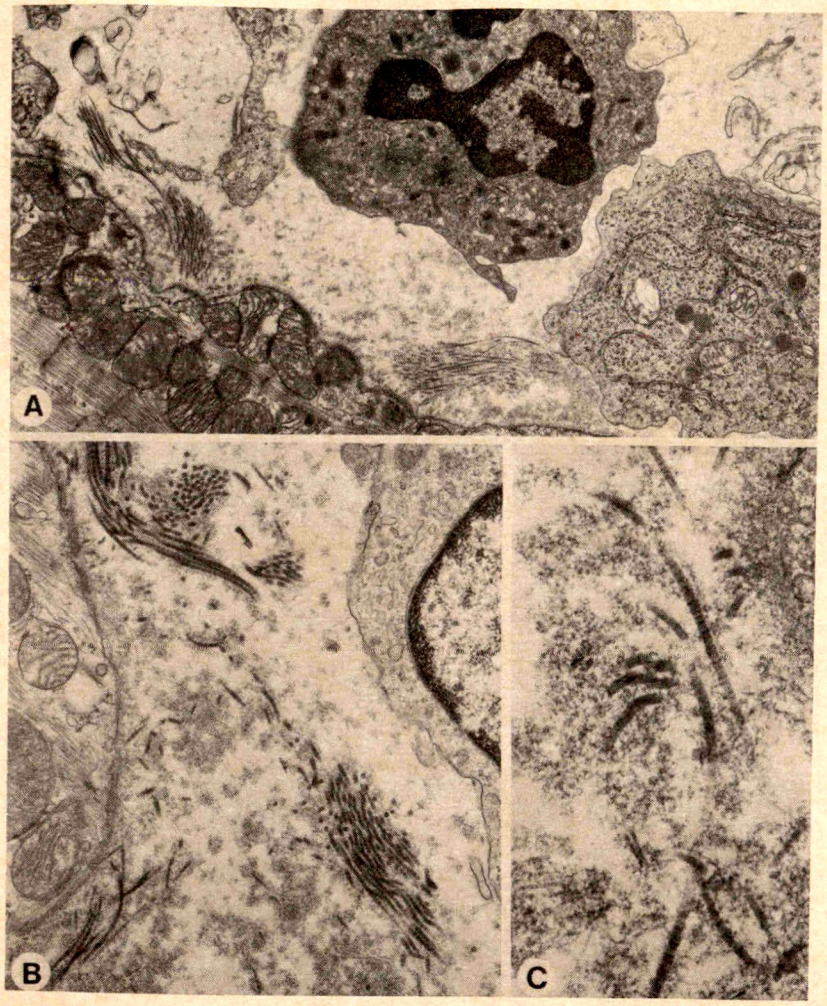

FIGURE 4. Electron micrographs of 24-hour-old myocardial infarcts from control (non-irradiated) rats. Compare with Figure 3 d–f. **A,** a polymorphonuclear neutrophil (**upper center**) and a macrophage (**lower right**) are present in border zone area with interstitial edema. Disruption of collagen bundles has occurred, even though the cardiac muscle cell is not necrotic. Magnification × 13,850, reduced 36%. **B,** higher-magnification view of area similar to that shown in A. The collagen fibrils are surrounded by connective tissue microfibrils and finely granular material of low electron density. Magnification × 19,400, reduced 36%. **C,** high-magnification view of disrupted collagen fibrils, which appear coarsely granular and terminate into masses of granular or amorphous material. Magnification × 46,500, reduced 36%.

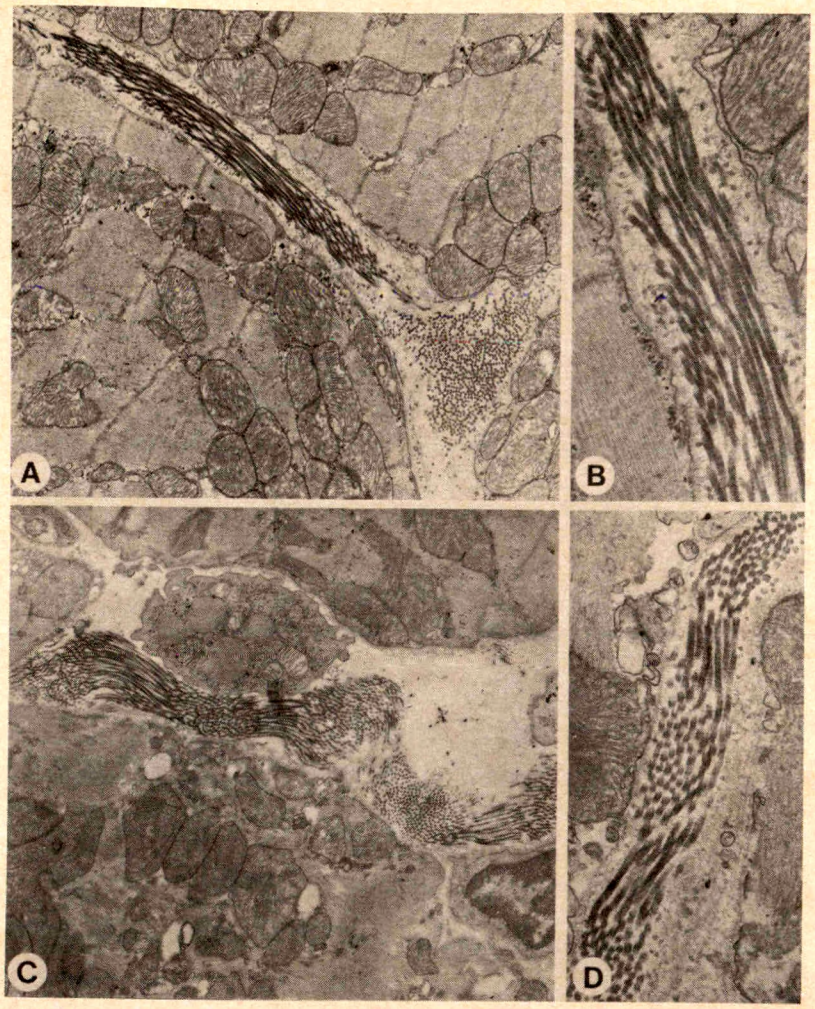

FIGURE 5. Electron micrographs of 24-hour-old myocardial infarcts from irradiated rats. Compare with Figure 3 a–c. **A,** two bundles of collagen fibrils separating nonnecrotic muscle fibers in border zone appear normal. Magnification × 14,650, reduced 36%. **B,** higher-magnification of view of part of normal collagen bundle shown at upper left in A. Magnification × 29,850, reduced 36%. **C,** normal collagen bundle is adjacent to disrupted severely necrotic myocyte (**lower left**). Magnification × 13,150, reduced 36%. **D,** normal collagen bundle separates 2 necrotic myocytes with fragmented plasma membranes. Magnification × 24,900, reduced 36%.

to the transmural infarct. In serial studies of rat myocardial infarcts, Fishbein et al[15] showed that significant fibroblast infiltration and collagen deposition are not seen until the third day after infarction. This suggests that there is a period during which the tensile strength of the infarct margin may be greatly reduced, rendering it vulnerable to thinning or rupture. Although cardiac rupture was not noted in any rats in this study, the analogy to human MI cannot be dismissed. Human infarcts demonstrate an even more intense polymorphonuclear leukocyte response than do those in rats. Serial studies of human infarcts have demonstrated that fibroblastic infiltration does not begin until 4 days after infarction, with collagen deposition occurring during the second week.[16,17] Thus, human transmural infarcts may be exposed to an even more prolonged vulnerable period between proteolysis of preexisting collagen and deposition of new collagen in the region of the infarct.

The demonstration of inflammatory cell proteases mediating infarct wall collagen degradation may have important therapeutic implications for the prevention of cardiac rupture, which still has a 10 to 20% incidence among fatal acute myocardial infarctions.[18,19] The administration of anti-inflammatory agents early after infarction, when inflammation is initiated at the infarct margin, might protect the collagen fibroskeleton from proteolysis.[20] A recent report, however, has indicated that ibuprofen actually leads to an increased incidence of scar thinning after MI in dogs.[21] Interference in the normal leukocyte degradation of necrotic tissue might be harmful, despite protection of collagen. Further experiments are being performed to clarify this issue.

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Assessment of Quantitative Methods for 2-Dimensional Echocardiography

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Several 2-dimensional echocardiographic (2-DE) methods were tested in vitro for accuracy of linear and cross-sectional measurements and in vivo for left ventricular (LV) volume reconstruction. With 2-DE instrument settings at low and high gains and with precise in vitro calibrations, we studied myocardial slice thickness (3.0 to 10.0 mm). The 2-DE myocardial thickness was measured by leading-trailing, trailing-leading, and leading-leading methods. Regression analysis of 2-DE versus direct measurements yielded excellent correlations for all 3 methods ($r > 0.985$), with interobserver variability $< 3\%$. Accuracy of measurement was satisfactory only for the leading-leading method (3 and 6% error at low and high gains, respectively); other methods substantially over- or underestimated thickness. Thin myocardial slices (<1 mm thick) were applied to cylinders and fixed in formalin to produce precise cavity areas (1.8 to 7.0 cm^2). Regression analysis of 2-DE versus actual cavity area gave high correlations ($r > 0.970$), and low interobserver variability ($< 4\%$) for the inner edge and leading edge methods, but the leading edge method was the most accurate (1.3 to 2.5% error). In vivo LV volumes in 7 anesthetized dogs were compared with 2-DE and cineangiography. Good correlations ($r = 0.92$) were obtained, but the inner edge method underestimated angiographic volume, whereas the leading edge method reduced the magnitude of underestimation. Thus, the leading edge method for 2-DE is most accurate not only for linear and cross-sectional measurements of the myocardium, but also for application to in vivo LV volumes.

Previous studies with 2-dimensional echocardiography (2-DE) have shown that reasonable estimates for left ventricular (LV) volume and mass can be obtained in both dogs[1–7] and man.[8–10] Nevertheless, direct quantitative assessment has been impeded because echocardiography generally underestimates volumes compared with cineangiography.[6,8,10] In a recent study,[11] 2-DE underestimated short-axis cavity area of the formalin-fixed heart. The reasons for these discrepancies are not certain, but they could result partially from an inappropriate method of measurement from the echocardiographic images. Basic measurements of LV dimensions and cross-sectional areas are required to adequately validate the most accurate method for echocardiographic measurement. Thus, the objectives of this study were (1) to determine in vitro the most accurate echocardiographic method for performing linear and cross-sectional measurements, and (2) to apply and test this method for determining LV volume in the beating heart.

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Methods

In vitro studies: Three mongrel dogs were killed with an overdose of pentobarbital sodium. The hearts were removed and frozen. Using a Burkholt meat slicer, the frozen canine myocardium was sliced into sections 3 to 10 mm thick. With a calibrated needle, the thickness of each section was measured directly to the nearest 0.2 mm in a minimum of 4 locations per section. Only sections with exactly corresponding measurements in each location were used for echocardiographic study. The frozen myocardium was further sliced into long tissue sections <1 mm thick; these were wrapped around and secured with thread to 4 plastic syringe cylinders fixed in formalin and then removed from the syringe for subsequent 2-DE study. The cut end of each syringe and 1 end of each myocardial cylinder was photographed. Actual intraluminal cross-sectional area of the cylindrical standards was measured

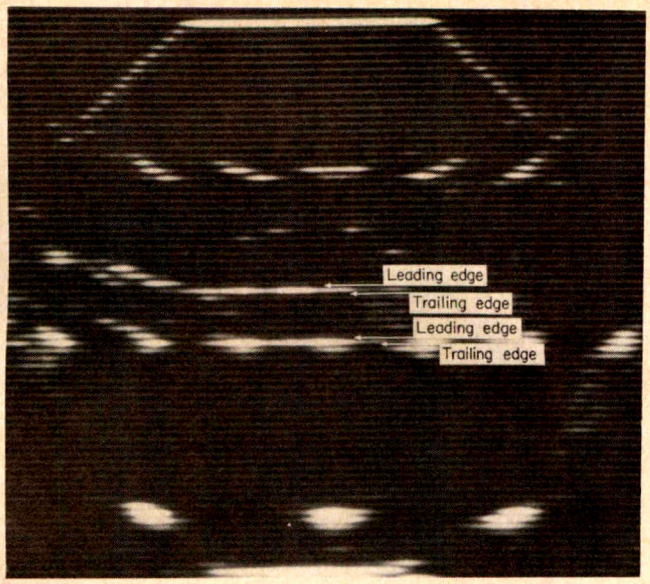

FIGURE 1. Two-dimensional echocardiographic low-gain image of a slice of myocardium interposed in the calibration box. Leading and trailing edges are designated for both upper and lower echo interfaces of the myocardial tissue. Echo images of the calibration strings are also prominent.

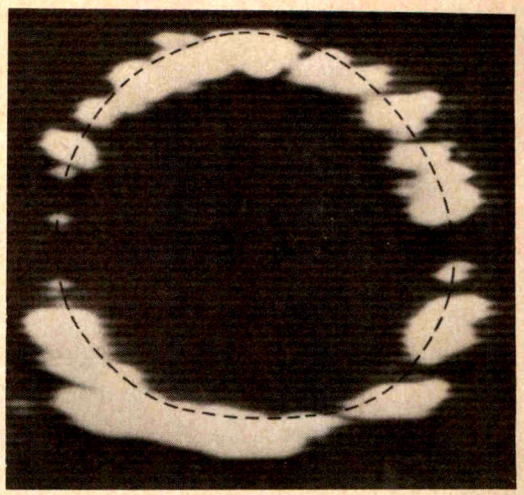

FIGURE 2. Two-dimensional echocardiographic image of a formalin-fixed cylinder of thin myocardium. **Broken line** within this image demonstrates the leading edge method. At the central top and bottom of the circle, the broken line lies at the leading edge of the image, but as the image blooms out laterally, this line is directed toward the center of the echo image. In contrast, the inner echo method would outline the inner border of the circular echo image for the entire circumference.

to the nearest 0.1 cm^2 by planimetry of photographic outlines; duplicate area measurements from both syringe (outer surface) and myocardial outlines corresponded exactly for the 4 sizes, 1.8 to 7.0 cm^2.

The myocardial frozen sections and the formalin-fixed cylinders were placed separately into a waterbath along with a calibration phantom box and imaged with a 90° mechanical sector scanner unit (ATL Mark III) over a wide range of electronic gain settings. Figure 1 shows a low-gain 2-DE image of a section of myocardium 6 mm thick. Both the upper and lower surfaces of the tissue exhibit echocardiographic interfaces, separated by the absence of echo between them. For each interface, leading and trailing edges are designated. Low gain was defined as the lowest possible setting at which tissue targets were well visualized, and high gain as a standardized number of incremental electronic gain settings. Low- and high-gain settings were produced by changing only the damping adjustment while other instrument parameters were kept constant. With stop-frame analysis of 2-DE images, myocardial thickness was measured directly from the screen by 3 commonly used methods: (1) The leading-trailing method measures thickness from the leading edge of the upper echo to the lower echo interface, and therefore includes the width of both echo interfaces. (2) The trailing-leading method measures thickness from the trailing edge of the upper echo interface to the leading edge of the lower echo interface, and excludes the width of both echo interfaces. (3) The leading-leading method measures thickness from the leading edge of the upper echo interface to the leading edge of the lower echo interface, and includes the width of only the upper echo interface.

The 2-DE low- and high-gain images of the formalin-fixed cylinders of myocardium (Fig. 2) were traced using a wax pencil with a video overlay technique using 3 methods: (1) The inner edge method, which is the most commonly used, outlines the inner border of the circular echo image all along the circumference. (2) The leading edge method is shown by the broken line in Figure 2; at the point closest and farthest from the echo transducer corresponding to the central top and bottom of the circular echo image, the broken line is at the leading edge, but as the circle is followed toward its lateral margins, the broken line is drawn toward the center of the echo signature. (3) A mid-echo method follows the center of the echo width along the entire circumference. Cross-sectional areas were determined from the circular tracings by means of planimetry. Both the echo transducer and the objects were in fixed positions during the change of gains. Increasing gain was associated with receding trailing edges, blooming lateral edges, but stationary leading edges confirming the adequacy of a leading edge methodology just described and outlined in Figure 2. Although in vitro cylindrical wall thickness (<1 mm) is negligible with regard to 2-DE axial resolution, in vivo LV wall thickness (>5 mm) is substantial. Figure 3 demonstrates the appropriate in vivo tracing methods.

Comparison of 2-DE with direct in vitro measurements was performed by linear regression and percent error analyses of both thickness of myocardial section and area of myocardial cylinder. For each method, an average of duplicate measurements by 1 observer was compared with the in vitro measurement. Each individual percent error of measurement was calculated as follows: error (%) = direct − 2-DE/direct × 100. The average percent error was determined as the mean of the absolute individual error determinations, 8 for thickness (Fig. 3) and 4 for area (Fig. 4).

In vivo studies: Seven mongrel dogs (24 to 35 kg) were anesthetized with intramuscular morphine (1.5 mg/kg) and intravenous pentobarbital sodium (30 mg/kg). Respiration was maintained with room air using a Harvard respirator pump. Placement of catheters, 2-DE examination according to the method developed and extensively used in our laboratory, and cineventriculography were accomplished in this closed-chest preparation in the control state. Figure 3 shows a typical 2-DE systolic short-axis image at the mid-papillary level of an in vivo canine left ventricle with a demonstration of the tracing methods for endo- and epicardium.

Single-plane cineangiography was performed 5 to 10 minutes after 2-DE to eliminate differences in heart rate. The dog was placed on its left side in a right anterior oblique rotation.[12]

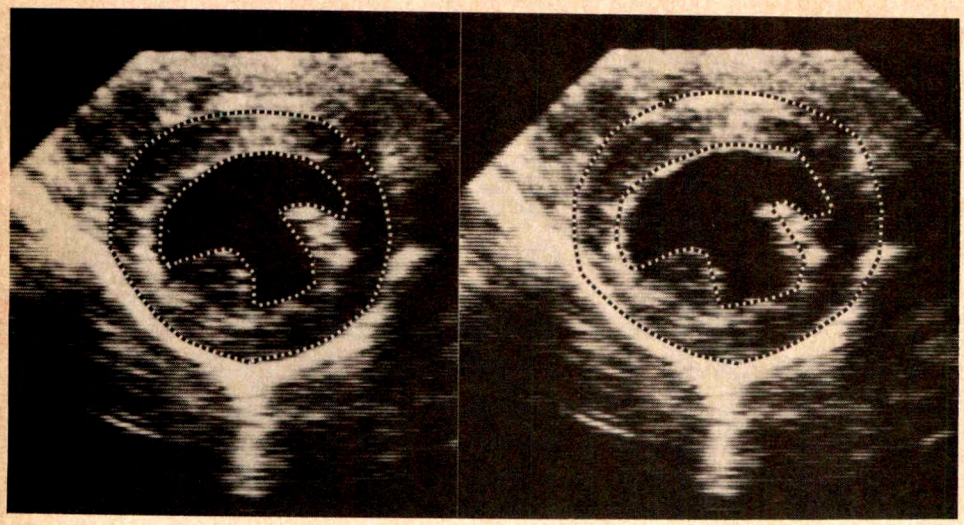

FIGURE 3. Typical 2-dimensional echocardiographic short-axis image of the mid-papillary level of the in vivo left ventricle of a closed-chest dog (at end-systole). **Broken lines** demonstrate the inner edge tracing method (**left**) and the leading edge tracing method (**right**).

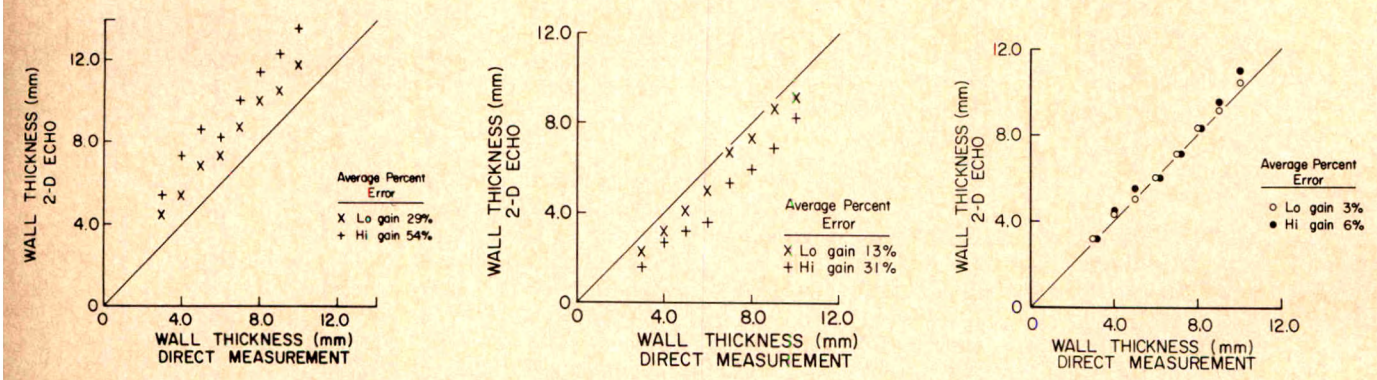

FIGURE 4. Comparison of in vitro myocardial thickness measurements, direct (x-axis) versus 2-dimensional echocardiography (2-D Echo) (y-axis) with (**left**) leading-trailing, (**middle**) trailing-leading, and (**right**) leading-leading methods in the presence of low gain (x or o) and high gain (+ or ●). Average percent errors are listed for low (Lo) and high (Hi) gains. The identity line is indicated by a **solid line.** Linear regression equations for the data are as follows: Lo gain (a) $y = 1.03x + 1.41$, (b) $y = 1.03x - 0.89$, $y = 1.02 + 0.23$; Hi gain (a) $y = 1.10x + 2.46$, (b) $y = 0.91x - 1.21$, (c) $y = 0.97x + 0.60$.

LV injection of 50% Hypaque® solution (1 ml/kg) was performed through a #7Fr pigtail catheter and synchronized with the electrocardiogram for early diastole. Ventriculograms were recorded at 30 frames/s on 16-mm film. The left ventricle was adequately opacified in all dogs at the time of the second or third beat after the start of injection. Outlines of the left ventricle were traced from the frame immediately preceding the onset of contraction, determined by visual comparison (end-diastolic volume), and the frame with the smallest intraluminal area, before opening of the mitral valve (end-systolic volume). LV volumes at both end-diastole and end-systole were computed using the standard formula, assuming geometry of an ellipsoid of revolution. This volume was corrected by means of the Bentivoglio regression equation.[12] No measurements were made during ectopic or postectopic beats.

Data analysis: For 2-DE LV volumes, both the Simpson and the 5/6 short-axis area multiplied by the length reconstruction formula[2,4] were used, and results were compared with determination of volumes by cineangiography. Linear regression analysis was performed using the least-squares method, and standard error of the estimate was calculated.

Reproducibility of echocardiographic measurements: In vitro myocardial thickness and cavity area measurements were performed by 2 trained observers who independently selected, traced, and measured their own frames from the audiovisual tape recording. Average percent error between the 2 observers was calculated separately for low- and high-gain settings.

Results

In vitro studies: Figure 4 shows plots for direct measurement of myocardial thickness on the x-axis versus 2-DE measurements of thickness on the y-axis for the 3 echocardiographic methods of measurement (see Methods section). For all 3 methods, linear regression analysis gave excellent correlation coefficients at low gain, 0.995 to 0.996, and only slightly lower results at high gain: 0.993 for leading-leading, 0.991 for trailing-leading, and 0.985 for leading-trailing. Average percent error of direct myocardial thickness determinations versus 2-DE measurements differed dramatically for these 3 methods (Fig. 4). Regression equations are listed in the legend. With the leading-trailing method (Fig. 4, left), 2-DE consistently overestimated myocardial thickness, all points lying above the identity

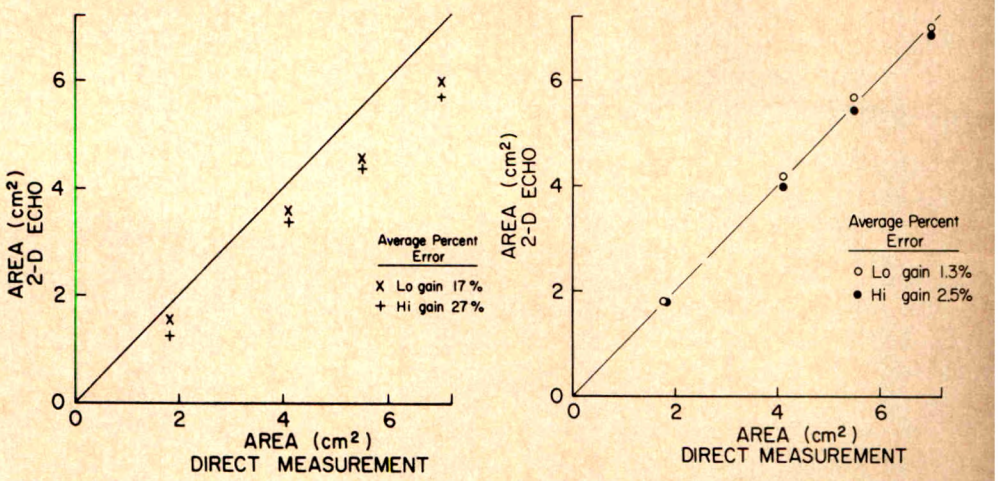

FIGURE 5. Comparison of in vitro myocardial cylindrical area measurements, direct (x-axis) versus 2-dimensional echocardiography (2D Echo): (**left**) inner edge and (**right**) leading edge methods in the presence of low gain (x or o) and high gain (+ or ●). Average percent errors are listed for low and high gains. The identity line is indicated by a **solid line.** Abbreviations are the same as in Figure 3. Linear regression equations for the data are as follows: Lo gain (a) $y = 0.87x - 0.18$, (b) $y = 0.99x - 0.18$; Hi gain (a) $y = 0.87x - 0.55$, (b) $y = 0.99x + 0.01$.

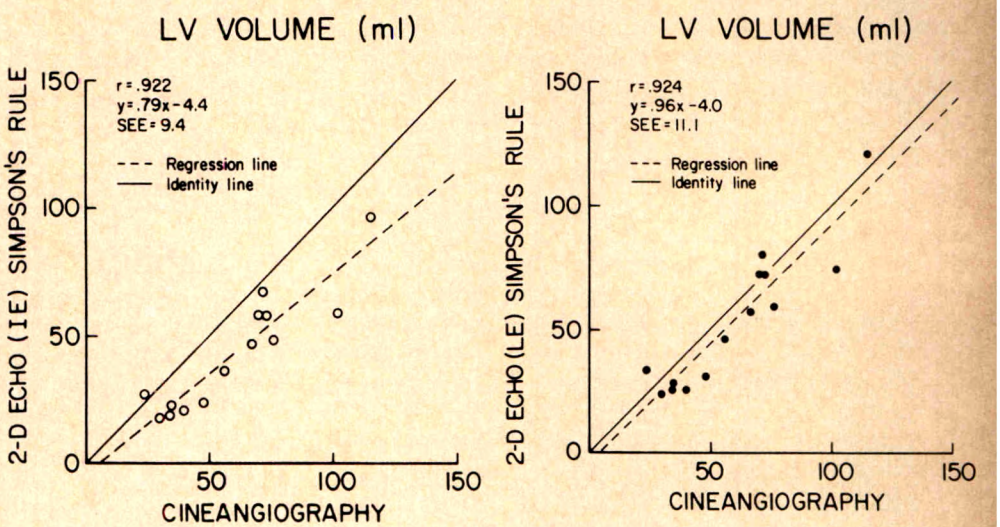

FIGURE 6. Comparison of left ventricular (LV) volume determinations, cineangiography (x-axis) versus 2-dimensional echocardiography (2-D Echo) (y-axis) with (**left**) inner edge (o) and (**right**) leading edge (o) methods. LV volumes were determined at end-diastole and end-systole by a Bentivoglio[12] regression equation for cineangiography. Linear regression analysis was performed; the correlation coefficient (r), regression equation, and standard error of estimate (SEE) are listed. Regression and identity lines are shown. IE = inner edge method; LE = leading edge method.

line. Average percent error calculation indicated a 29% overestimation for low gain and a much greater (54%) overestimation for the high-gain setting. With the trailing-leading method (Fig. 4, middle), 2-DE consistently underestimated myocardial thickness, all points lying below the identity line. Average percent error indicated a 13% underestimation for low gain and a 31% underestimation for the high-gain setting. In contrast, with the leading-leading edge method (Fig. 4, right), data points were distributed on or near the identity line and the average percent error was quite small, only 3% for the low-gain and 6% for the high-gain setting.

Figure 5 shows graphs similar to those in Figure 4 but involving measurements of cross-sectional cavity areas. Regression equations are listed in the legends. With the inner edge (trailing-leading) method (Fig. 5, left), points are distributed below and to the right of the identity line, indicating a consistent underestimation of cross-sectional area by 2-DE. Although the correlation coefficients are excellent, 0.988 for low and 0.999 for high gain, the average percent errors were quite high, 17 and 27%, respectively. In contrast, with the leading edge method (Fig. 5, right), points are distributed near and on either side of the identity line, indicating a close estimation of area by 2-DE. Computed correlation coefficients were 1.000 for the low-gain and 0.998 for the high-gain settings, and average percent errors were very low—1.3 and 2.5%, respectively. From the regression equations, one observes intercepts near 0 but slopes that are nearer 1.0 for the leading edge (0.99) than for the inner edge (0.87) method. Corresponding percent errors for the "mid-echo" method were 2.5% for the low-gain and 9.1% for the high-gain setting, whereas correlation coefficients were above 0.980.

In vivo studies: Figure 6 shows plots of LV volumes at end-diastole and at end-systole for 2-DE versus angiography in 7 dogs. 2-DE volumes were calculated by Simpson's rule for serial short-axis areas and length, the short-axis myocardial sections being traced by the inner edge (trailing-leading) method (Fig. 6, left) and leading edge method (Fig. 6, right). Linear regression analysis revealed good correlation coefficients of 0.92 for both methods and similar values for intercept and variability. However, the slope is substantially higher for leading edge (0.96 versus 0.79), similar to the in vitro cavity area slope comparison (0.99 versus 0.87). Examination of the

graphs shows that the use of inner edge methodology results in a greater and more consistent underestimation of LV volume than does the use of leading edge method; this difference is evident in the lower average percent error for leading edge (10 versus 17%).

Similarly, the LV short-axis area-length formula[2] gave good linear correlations (>0.860) for both tracing methods, but the inner edge method gave a greater, more consistent underestimation of volume than did leading edge method (12 versus 9%).

Interobserver reproducibility of echocardiographic measurements: For myocardial thickness measurements, slightly smaller average percent errors were observed with the leading-leading method (3 and 6% for low and high gains, respectively); values for other methods ranged up to 10%. For cavity area measurements, average percent errors were quite small, 2 and 3%, respectively, for both inner edge (trailing-leading edge) and leading edge methods. For 20 in vivo LV short-axis area measurements, average error between observers was not significantly different for leading and inner edge methods, 5.9 ± 0.9% versus 5.7 ± 1.4% (mean ± standard error of the mean), respectively.

Discussion

This study of quantitative 2-DE examines the accuracy of several methods of obtaining unidimensional and cross-sectional measurements. To obtain satisfactory direct tissue measurements, myocardium was sliced into appropriate frozen or formalin-fixed sections. The use of sliced myocardium with smooth, regular surfaces was required to facilitate precise and direct measurement and also to avoid errors encountered when attempting to rationalize the location of the echo beam in tissue with irregular surfaces. Thin myocardium (<1 mm thick) was applied for constructing precise cylinders with a single interface in the echo image, avoiding complications resulting from double interfaces. With this in vitro approach, only a leading edge 2-DE measurement method provided consistent accurate estimation of thickness and cavity area at both low- and high-gain settings (1.3 to 6.0% error). Other commonly used echocardiographic methods of measuring myocardial thickness resulted in either substantial overestimations (leading-trailing or standard convention) or understimations (trailing-leading or Penn convention). Leading edge area measurements showed low percent errors despite the fact that some arbitrary judgment was required in estimating the leading edge crossover in the lateral portions of the circle (Fig. 2); interobserver variability was only about 6%. The commonly used inner edge (trailing-leading) echo method for cross-sectional area measurement consistently underestimated the direct area measurement.

The features of a 2-DE short-axis image of the left ventricle may vary substantially, depending on the type of echo machine used and the gain settings. The difference between leading edge and inner edge delineations would tend to be greater in images with broader echo interfaces. Garcia et al[13] previously described computerized algorithms for performing correction from the conventional inner edge (trailing-leading) to the leading edge method for delineation of endocardial borders in 2DE short-axis images.

Previous studies with M-mode echocardiography showed that reasonably good estimations of LV mass can be obtained with wall thickness being measured by leading-trailing or trailing-leading methods.[14–16] Because wall thickness varies widely throughout the left ventricle, only an average wall thickness is required for calculating LV mass. Consequently, a good estimation of mass does not necessarily imply accurate measurements of wall thickness. Devereux and Reichek[14] stated that even though the trailing-leading method gave the best estimate of average wall thickness for LV mass determination, it could not be judged whether it was due to increased accuracy of measurement or just fortuitous compensation of factors.

Because the endocardial surface of the beating heart is not smooth, but highly irregular because of trabeculae and papillary muscles, practical application of the leading edge method might not be as simple as that with in vitro smooth surface objects. To investigate this problem, LV volume was determined by 2-DE in 7 dogs and compared with LV volume obtained by cineangiography. Previous studies in the beating heart have shown good correlations but consistent volume underestimation[6,8,10] with a 2-DE inner edge method. In the current study, similar observations were made in 7 dogs, but additional observations with a 2-DE leading edge method indicated consistently closer estimations of angiographic LV volume than those with inner edge method. For leading edge versus inner edge method, regression slopes were nearer 1.0 with both in vitro cavity area (0.99 versus 0.87) and in vivo LV volume (0.96 versus 0.79), whereas correlation coefficients, intercepts, and variability were similar for the 2 methods. Although cineangiography as an indirect method for estimating LV volume does not provide a perfect reference standard,[17] the consistency of results from in vitro to in vivo phases of the current study suggests the adequacy of angiography as a reference standard for LV volume and tends to confirm the superior adequacy of the leading edge method for in vivo as well as in vitro applications. The small 2-DE underestimation of angiographic LV volume with the leading edge method might be attributed to inherent differences between angiographic and echocardiographic techniques.[17] First, injection of contrast material may increase actual LV volume during cineangiography. Second, LV endocardial image projection with 2-DE may represent the surface of trabeculae, whereas in cineangiography a deeper silhouette contour may be imaged because contrast material enters the spaces between the trabeculae. For these reasons, LV volume estimation by cineangiography would be expected to slightly exceed that of 2-DE. Bommer et al,[18] using directly measured volume standards, recently demonstrated that estimations of volume by angiography and 2-DE are comparably accurate.

Correlation coefficients for angiographic versus echocardiographic comparisons in this study were quite close to those observed in a previous study (r = 0.92 for Simpson's rule, r = 0.87 for the bullet formula).[6] Thus,

the leading edge method may be well suited for LV volume determination from 2-DE images of the beating heart, in which the endocardial surface is quite irregular. This observation may be due to the averaging effect in determining LV volumes from short-axis areas. However, precise 2-DE measurement of wall thickness at any given point in the LV wall may be complicated by irregularities in the LV endocardial surface.

In summary, study of ultrasonic images obtained with 2-DE indicates that a leading-to-leading edge method may be most accurate for linear and cross-sectional measurements of the heart and also for LV volume determination.

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Chapter in Book: Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968: 134–139.

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2. Pulse Width	✓		✓		✓			✓
3. Pulse Amplitude	✓		✓		✓			✓
4. Sensitivity	✓			✓	✓			
5. Refractory	✓				✓			
6. Hysteresis	✓				✓			
7. Mode	✓		✓		✓		✓	
"Measured" Data								
1. Rate		✓	✓		✓	✓	✓	
2. Pulse Current				✓	✓		✓	✓
3. Pulse Voltage			✓	✓	✓		✓	✓
4. Pulse Energy				✓			✓	✓
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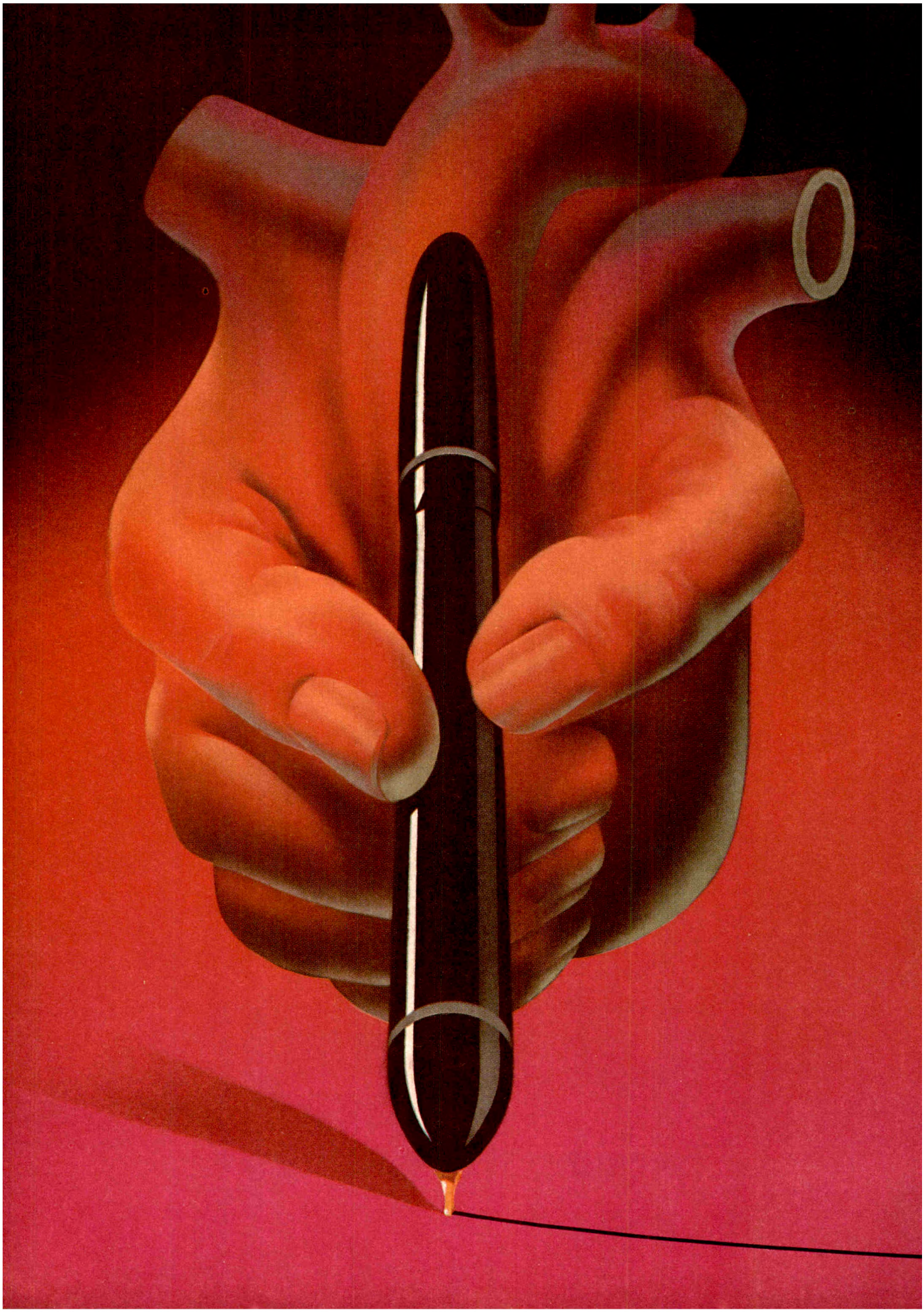

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WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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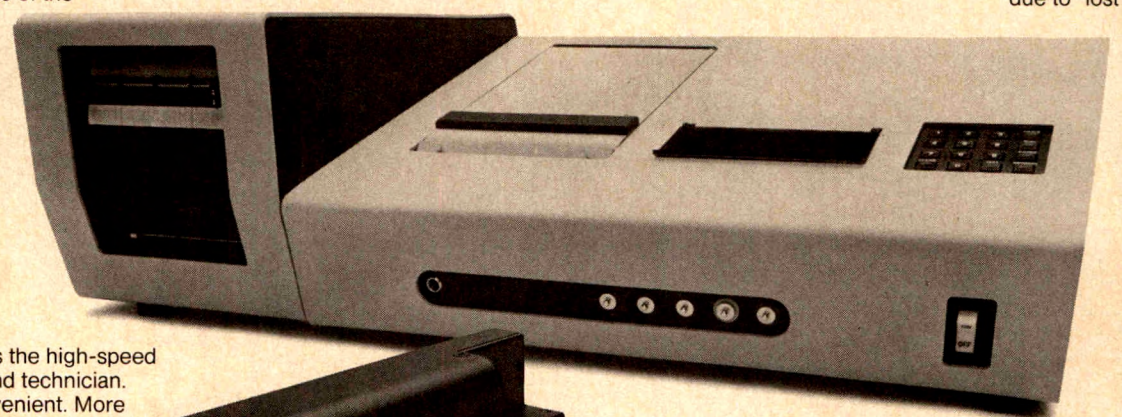

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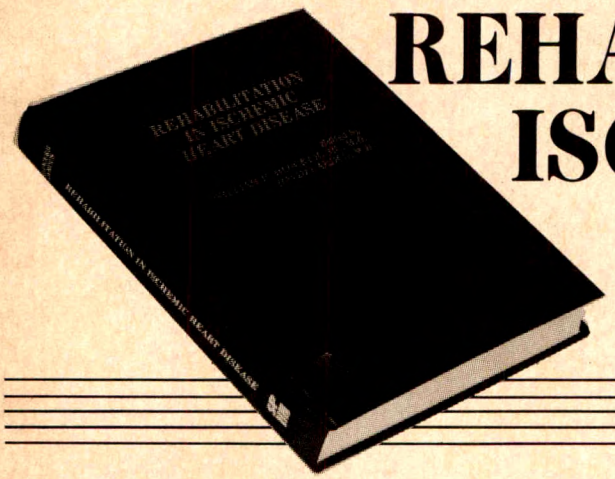

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Heavily illustrated, this volume presents 60 self-contained chapters dealing with *all* aspects of rehabilitation of the patient with ischemic heart disease. The 45 noted contributors discuss topics such as: designing a cardiac rehabilitation center; methods of rehabilitation for the stroke patient, amputee, spinal cord injury patient who has had a heart attack; equipment needs for a cardiac rehabilitation center; and legal responsibilities of the physicians and therapists.

All major aspects, from epidemiology and pathogenesis through prevention and education are covered, including ambulatory monitoring of electrocardiogram and blood pressure; evaluation of degree of disability; and pathogenesis of atherosclerosis. This book contains the *most complete* list of cardiac risk factors to be found in any text. This encyclopedic guide to the total care and rehabilitation of cardiac patients is written for *every* member of the cardiac rehabilitation team.

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Synopsis of the Symposium

Step 1: Nitrates

Since nitrates both reduce myocardial oxygen demand and increase myocardial oxygen supply, their use is warranted as initial therapy for the control of angina pectoris. Dosage needs often vary significantly from patient to patient, and attention should be given to ensure that an adequate dosage level has been established.

Step 2: Nitrates and beta blockers

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Step 3: Nitrates and calcium antagonists

Calcium antagonists have special usefulness in controlling cases where the myocardial oxygen supply is diminished by coronary vasospasm; their use in combination with nitrates is recommended if Step 2 therapy is unsatisfactory (or if the patient has variant or vasospastic angina).

Consensus of the Symposium

Nitrates are basic in step-care therapy for ischemic heart disease

Step 1
Stable or unstable angina: Nitrates

Step 2
If not controlled: Nitrates + beta blockers

Step 3
If still not controlled (or in variant angina): Nitrates + calcium antagonists

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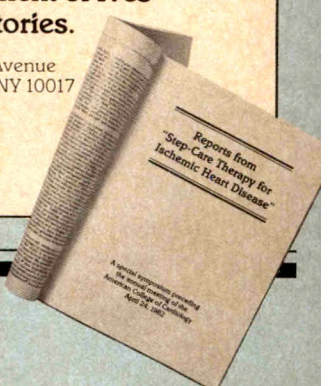

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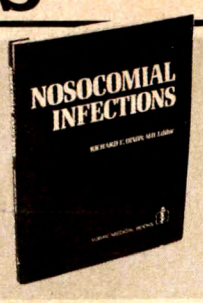

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The First Human Heart Defibrillation

LESLIE A. GEDDES and ROBERT HAMLIN

In 1947, Beck et al[1] reported the first successful defibrillation of the human heart. Stating that "ventricular fibrillation occurs as a terminal arrhythmia in 50 percent of patients" (citing a paper that they were preparing), they continued, "If ventricular fibrillation develops in hearts that are relatively normal, especially during operation, defibrillation may be lifesaving." In 1937, Beck and Mautz[2] reported the development of this technique in dogs, in which defibrillation had been accomplished after 30 minutes of open-chest cardiac massage and artificial respiration.

The opportunity for the human application occurred in association with a 14-year-old boy who had been admitted for sternal resection. Beck wrote:

> During the induction of the nitrous oxide and ether anesthesia, on the sixth hospital day, the pulse rate rose to 160 per minute and remained at this level for forty-five minutes. After the administration of 1.6 mg. of lanatoside C the rate returned to 80 per minute, where it remained during most of the two hours required for completion of the operation. There were no other unusual circumstances attending the procedure.
>
> During the closure of the wound in the chest, the pulse suddenly stopped and the blood pressure sounds could not be heard. The patient was apparently dead.

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The wound was reopened and cardiac massage immediately was initiated, 1 mg. of epinephrine given intravenously and more lanatoside C administered with no visible or responsive effects. The mechanical respirator was attached to the intra-tracheal tube and cardiac massage continuously given for the next thirty-five minutes, at the end of which time the electrocardiogram (fig 1a) was characteristic of ventricular fibrillation. Another record ten minutes later was recorded just prior to the first electric shock applied directly to the heart (fig 1b). This record, as well as the tracing recorded immediately after the first shock, also showed ventricular fibrillation. Since the first shock was unsuccessful, procaine hydrochloride was injected into the right auricle, the heart massaged and a second series of shocks given. The heart then was in standstill.

Almost immediately, however, feeble, regular and fairly rapid cardiac contractions were seen, but massage was continued for five more minutes, at which time it was obvious that contractions were coordinated and fairly vigorous, though still fast. An electrocardiogram taken at this time revealed a supraventricular tachycardia at a rate of 175 (fig 1c). From this point on the heart gradually increased in vigor and brachial sounds were heard at 50 mm. of mercury. It is of more than passing interest to note that in spite of the critical condition of the patient and the apparent hopelessness of the situation, at no time was cyanosis or pupillary dilation present. This demonstrates that massage of the heart had maintained an adequate circulation.

After the coordinated heart beat had been established for twenty minutes, the wound in the chest was closed. Within ten minutes after closure of the wound the intra-tracheal tube was removed and respirations were

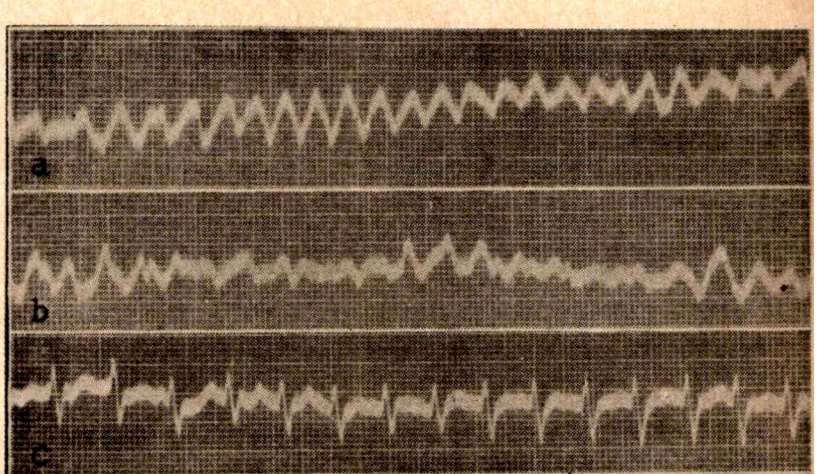

FIGURE 1. **a,** electrocardiogram showing coarse fibrillation; **b,** the immediate preshock electrocardiogram 10 minutes later; **c,** electrocardiogram after shock defibrillation.

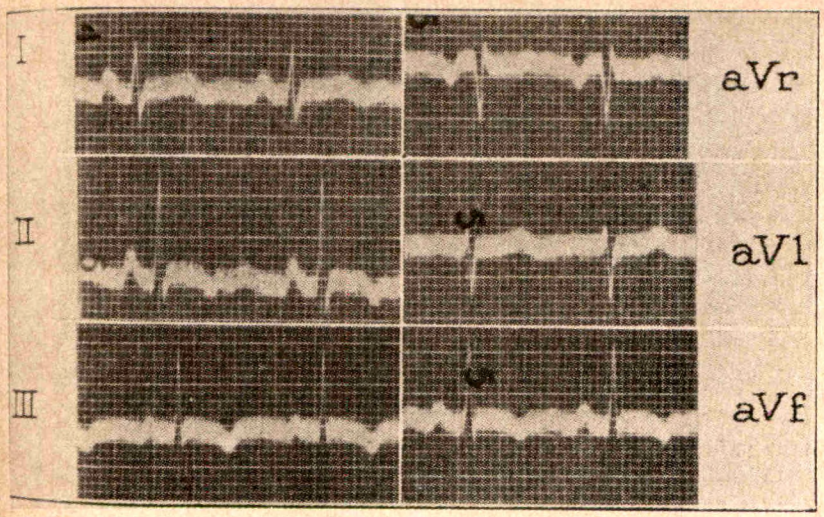

FIGURE 2. The frontal-plane electrocardiogram 2 months after operation.

resumed. Within one and one-half hours the blood pressure rose to 60 systolic and 40 diastolic, and thereafter it showed a steady, gradual rise to 100 systolic and 70 diastolic. Three hours after defibrillation of the ventricles, the patient responded rationally to questioning, and by eight hours he was fairly alert in spite of his stormy operation course.

The convalescence for the next few days was chiefly characterized by signs of digitalis intoxication and moderately severe azotemia, the nonprotein nitrogen reaching 100 mg. per hundred cubic centimeters on the second postoperative day. Within eight days, however, the patient was much improved, digitalis induced coupling having disappeared and the blood urea nitrogen having returned to 18 mg. per hundred cubic centimeters.

During the remaining seventeen hospital days, there were no symptoms or signs indicative of injury to the central nervous system, and he was discharged on his thirty-first hospital day. In a follow-up interview three months later, the patient stated that he had considerable increase in exercise tolerance. Electrocardiographic tracings at this time were normal (fig 2).

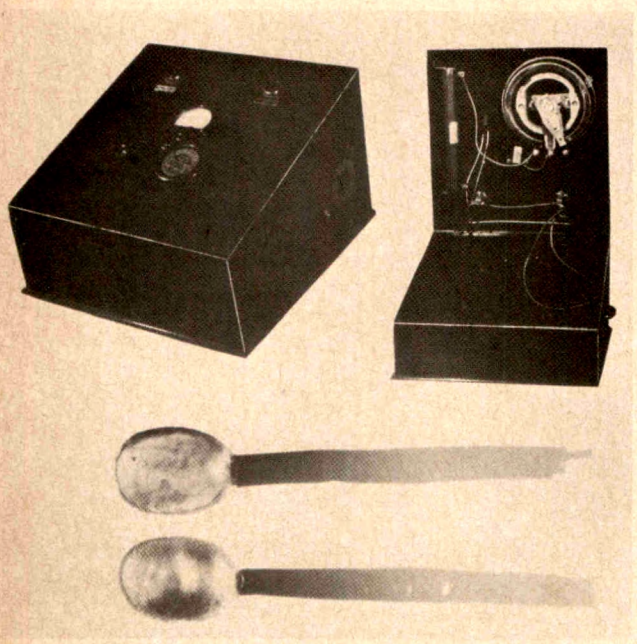

FIGURE 3. Beck's defibrillator with cover closed (**top left**) and open (**top right**); **bottom,** the electrodes, which were stored in the defibrillator cabinet.

Beck's prescription for defibrillation derived from his 1937 dog studies. He recommended: "An electrode preferably of silver, measuring about 25 square cm in area is placed on each side of the heart and an electric current is sent through the ventricles. The electrodes need not be padded to prevent burning if there is a large area of contact with the heart. The current is ordinary alternating current of 60 cycles and 1 to 1.5 amperes. The duration of the current is short, from 0.5 to about 2 seconds."

The defibrillator: Figure 3 is a photograph of Beck's defibrillator and electrodes, which were built by a friend, James Rand, an electrical engineer. The circuit diagram is shown in Figure 4 and reveals that the defibrillator consisted of an off-on switch, 2 pilot lights, a 10-ohm current-limiting resistor, a 25-ohm variable resistor (to enable setting the current), and a 0 to 5 ampere meter to indicate the current passing through the heart.

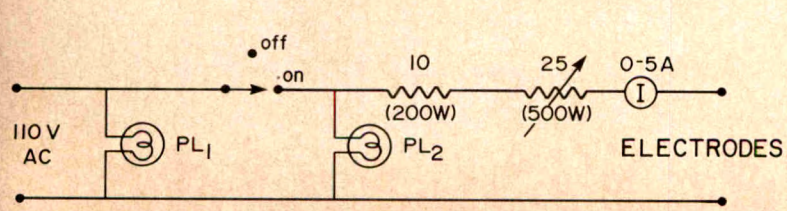

FIGURE 4. Circuit diagram of Beck's defibrillator which consisted of an off-on switch, 2 pilot lights, a 10-ohm current-limiting resistor, a 25-ohm variable resistor (to enable setting the current), and a 0 to 5-ampere meter (to indicate the current flowing through the heart).

With 28 ohms as a typical value of human heart resistance (Kerber et al[3] 1980), it is possible to estimate the typical maximum and minimum current that Beck could have used, which was as much as 2.8 or as little as 1.7 amperes. The corresponding energy values for a current flow of 0.5 second are 109 and 40 joules. Not long after, it was found that a current flow of about 0.2 second was adequate for defibrillation, thereby reducing the delivered energy by 60%.

So much interest was evidenced in Beck's success that he presented a monthly course on defibrillation during the years 1948, 1949, and 1950. On each of these occasions, some 2 dozen trainees fibrillated, massaged, and defibrillated the heart of a dog. The dog was recovered and presented to the class the next day.

Beck's defibrillator was duplicated by many investigators. Nine years later Zoll et al[4] used one with a higher output to accomplish closed-chest defibrillation. For the next decade alternating current was used and was displaced only when it was discovered that a single pulse of current could achieve defibrillation with the delivery of considerably less energy.

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Ratio of Regurgitant Volume to End-Diastolic Volume: A Major Determinant of Ventricular Response to Surgical Correction of Chronic Volume Overload

HERBERT J. LEVINE, MD, and WILLIAM H. GAASCH, MD

A most difficult decision in the management of patients with left ventricular (LV) chronic volume overload is when to proceed with valve replacement. There is, of course, a natural reluctance for clinicians to urge open heart surgery in asymptomatic or minimally symptomatic patients, yet among some patients with chronic aortic regurgitation (AR) or mital regurgitation waiting for clear symptoms of pulmonary venous congestion or a convincing effort syndrome may result in a disappointing response to corrective surgery. Symptomatic patients who survive operation without important perioperative complications (infection, thromboembolism, paravalvular leak, and so on) generally are fully or partially relieved of their symptoms. In asymptomatic as well as symptomatic patients, improvement or benefit can also be measured objectively (that is, reduction in heart size, regression of hypertrophy, improvement in exercise tolerance and ventricular function, and improved survival). In some patients, regardless of whether symptoms have improved, LV size and myocardial mass do not decrease significantly. These patients have a less good prognosis[1–4] and a considerable effort has been made to establish preoperative criteria for identifying this cohort of patients before surgery is performed.

The following preoperative markers of a suboptimal response to valve replacement in chronic AR have been suggested: (1) a large end-diastolic volume,[3,5,6] (2) a large end-systolic volume,[2,4,7–9] (3) an elevated end-diastolic pressure,[1,10] (4) a subnormal ejection fraction,[7–9,11–14] (5) increased indexes of systolic wall stress,[2,4,15] and (6) reduced exercise capacity.[16] Although some of these indexes are better than others in predicting the outcome of corrective surgery in patients with chronic AR, it remains difficult to identify with certainty the patients whose ventricular mass and dimensions will fail to diminish postoperatively.

Despite an extensive and varied approach to this problem, relatively little attention has been given to the magnitude of the regurgitant volume itself. Indeed, the regurgitant leak *is* the basis for both the hemodynamic abnormality and the clinical syndrome of valvular regurgitation, and elimination of the regurgitant volume is the primary effect of successful valve replacement. Thus, there is reason to believe that a quantitative assessment of the regurgitant volume may be helpful in predicting the response to valve replacement of a given patient with chronic valvular regurgitation. However, efforts to measure regurgitant volumes accurately have been thwarted by serious limitations in methods, and perhaps the inability to quantitate regurgitant flow with confidence has obscured the importance of this measurement. Nonetheless, with better techniques for measuring regurgitant volume, our ability to predict the response of the ventricle to valve replacement may be greatly improved.

An example of the importance of the absolute size of the regurgitant volume and its relation to the end-diastolic volume is illustrated in Table I. Consider 2 patients with symptomatic chronic AR. Both have the same heart rate, blood pressure, LV diastolic pressure and aortic valvular lesion (that is, same regurgitant valve orifice). One patient, however, has a slightly enlarged left ventricle with normal ventricular function; the other has a dilated myopathic ventricle. To simplify the comparison, both patients will be assigned the same total stroke volume (TSV) and regurgitant fraction (regurgitant fraction = regurgitant volume/total stroke volume).

In both patients, the magnitude of the regurgitant leak is the same, although ventricular size and function differ greatly. After successful aortic valve replacement,

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TABLE I Relative Volumes in Aortic Regurgitation

	Groups	
	A	B
End-diastolic volume index (EDVI) (ml/m^2)	100	200
Systolic ejection fraction	0.60	0.30
Total stroke index (ml/m^2)	60	60
Regurgitant fraction	0.50	0.50
Regurgitant stroke index (ml/m^2)	30	30
Regurgitant volume/end-diastolic volume	0.30	0.15
Postoperative EDVI (ml/m^2)	70	170

the regurgitant flow will be eliminated in both patients. Diastolic filling of the left ventricle will thus be reduced in both by an amount equal to the regurgitant stroke index (30 ml/m^2). Therefore, postoperative end-diastolic volume index (EDVI) in 1 (Group A patient) would be expected to be 70 ml/m^2, a reduction of 30%, whereas postoperative EDVI in patient 2 (Group B patient) will be 170 ml/m^2, a reduction of only 15%. Furthermore, because the fractional reduction in heart size will be less in the Group B patient, the "stimulus" to regression of hypertrophy also will be less, since wall stress is a linear function of chamber radius. The effect of eliminating regurgitant flow on LV filling pressure in both patients will be more difficult to predict, because the pressure-volume characteristics of the 2 ventricles certainly will be different. Nonetheless, because chamber compliance of the smaller ventricle will probably be less, the decrease in LV filling pressure will be proportionately less in the larger ventricle.

It is suggested, therefore, that the proportional reduction in heart size after aortic valve replacement is predicted by the ratio of regurgitant volume to end-diastolic volume. The implication of this assumption is that for a given amount of AR, the postoperative reduction in LV size and mass will be an inverse function of the end-diastolic volume. Not implicit in this analysis is that whereas regurgitant and end-diastolic volumes are "related" to one another, the end-diastolic volume of the ventricle has no *direct* influence on the size of the regurgitant volume.

Central to this issue is a clear understanding of the hemodynamic determinants of aortic regurgitant flow. As with turbulent flow across any orifice, pressure-flow relations across the aortic valve in diastole are defined by the Torricelli equation; that is, flow is proportional to the square root of the pressure gradient existing across the valve. Thus, the orifice equation, devised by Gorlin and Gorlin in 1951,[17] may be used to dissect the hydraulic factors that determine the regurgitant volume of a given lesion.

Determinants of aortic regurgitant volume: In the case of aortic valvular regurgitation, solving the orifice equation for aortic regurgitant stroke volume (ARV, ml) yields: $ARV = OA \cdot C \cdot Time_d \cdot \sqrt{P_1 - P_2}$, where OA = aortic regurgitant orifice area (cm^2), P_1 = aortic diastolic mean pressure (mm Hg), P_2 = LV diastolic mean pressure (mm Hg), $time_d$ = duration of diastole/beat (seconds), and C = constant.

There are, therefore, only 4 determinants of ARV: the size of the aortic valve orifice during diastole, the duration of diastole per beat (a function primarily of the heart rate) and the pressure in the aorta and left ventricle during diastole. Neither the forward stroke volume (or effective cardiac output) nor the size of the LV chamber have a *direct* bearing on ARV. It follows, therefore, that a large LV chamber does not mean that the regurgitant volume will be large. Indeed, under most circumstances, active enlargement of the ventricle is associated with an increase in filling pressures which would decrease rather than increase ARV.

Physiologic or pharmacologic manipulation of the constituents of the orifice equation, of course, will change regurgitant flow. For example, an increase in heart rate will reduce ARV by shortening diastole. Similarly, a venodilator that reduces left atrial and LV diastolic pressures more than it does arterial blood pressure can increase aortic regurgitant flow.

In addition to the primary determinants of regurgitant flow, each may be influenced secondarily by other hemodynamic variables. Changes in systemic vascular resistance, for example, may alter arterial diastolic pressure and, thereby, induce changes in ARV. Chamber volume, although not a primary determinant of regurgitant flow, will exert a secondary influence. In AR, chamber compliance of the left ventricle, a function of ventricular volume, will play a role in determining diastolic pressure and thus influence the size of the regurgitant volume. However, this will be so only through the mechanism of an altered diastolic pressure, not by virtue of the LV size as such. The difference between the 2 patients with AR illustrated in Table I lies not with the size of the regurgitant volume itself, but with myocardial factors that emerge as a consequence of the regurgitant volume.

Thus, among patients with chronic AR, while LV volume does not directly determine regurgitant volume, the immediate response of the ventricle to surgical correction of regurgitation will be influenced in a major way by the volume of the ventricle. The importance of this "immediate response" to valve replacement has been shown by serial echocardiographic studies performed soon after surgery. In a prospective echocardiographic study of the effect of valve replacement in patients with chronic AR, we[4,15] found that patients who achieved a substantial reduction in ventricular dimensions postoperatively did so before the time of the early postoperative study (7 to 10 days after surgery); little further reduction in LV size occurred during the course of the next 12 months. Similar observations have been made by others.[7,18–20] Furthermore, patients who did not achieve a significant reduction in LV size during the postoperative period had a less favorable outlook.[1–4]

To examine the hypothesis that the ratio of regurgitant volume to end-diastolic volume (RGV/EDV) determines the change in LV dimensions after aortic valve replacement, a prospective study is needed that would employ techniques capable of assessing the RGV/EDV

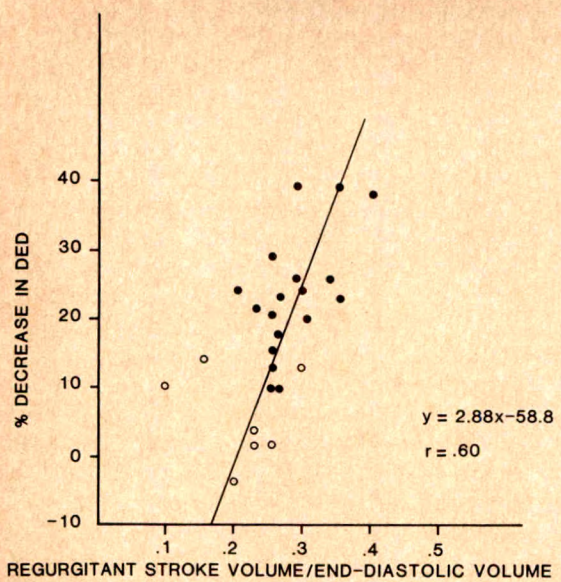

FIGURE 1. Early postoperative (7 to 10 days) percent decrease in left ventricular end-diastolic diameter (DED) as a function of the preoperative regurgitant volume/end-diastolic volume ratio. The **closed symbols** (Group A) represent patients whose end-diastolic diameter fell within the normal range (<3.3 cm/m^2) within 6 to 12 months after aortic valve replacement. The **open symbols** (Group B) represent patients whose end-diastolic diameter remained large (>3.3 cm/m^2) after aortic valve replacement.

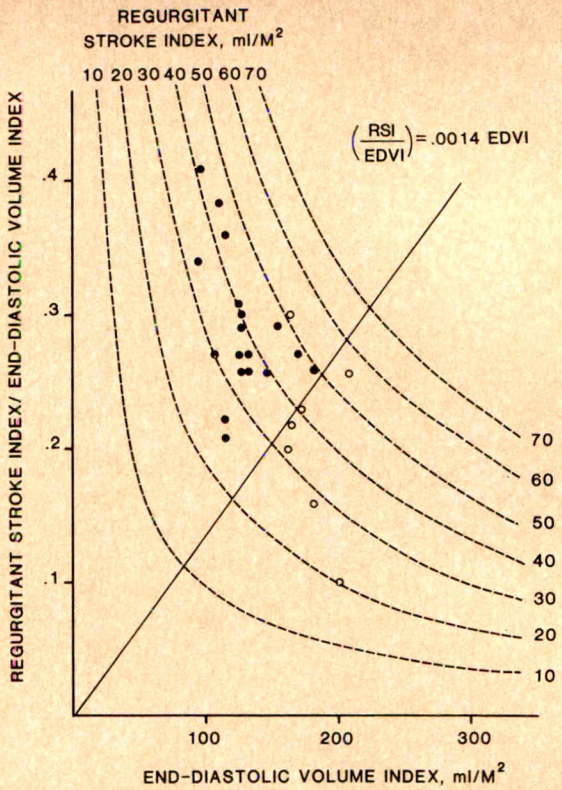

FIGURE 2. Regurgitant stroke index/end-diastolic volume index ratio (RSI/EDVI) as a function of the end-diastolic volume index. The **dashed lines** represent the isopleths of regurgitant stroke index. The **closed symbols** (Group A) and **open symbols** (Group B) are described in the legend of Figure 1. With the exception of 1 patient in Group B, Group A and Group B patients are clearly separated by this analysis.

ratio with confidence. A mechanism for doing so is provided by the fact that the RGV/EDV ratio may be expressed as the product of systolic ejection fraction and regurgitant fraction.* Because both of these latter measurements may be assessed by radionuclide techniques and neither is dependent on absolute volume calibration, an opportunity exists for tracking this index in patients with chronic volume overload using noninvasive techniques.

Pending the results of a prospective study, we sought to test the value of this hypothesis by a retrospective analysis of a group of 25 patients with chronic AR who underwent valve replacement and were reported previously.[4] In this analysis, preoperative echocardiograms were obtained near the time of cardiac catheterization and at 0.3, 3, 6, 9, and 12 months after surgery. LV end-diastolic volume, end-systolic volume and the calculated systolic ejection fraction were derived from the M-mode echocardiogram using the Teichholz volume formula[21] as: ventricular volume = $(7.0/(D + 2.4))D^3$, where D = echocardiographic LV internal dimension. Regurgitant fraction was determined from the LV stroke volume derived from the ventriculogram (30° right anterior oblique projection) and the forward stroke volume calculated using the Fick principle for oxygen. To compare pre- and postoperative LV dimensions, all absolute volume measurements were derived from echocardiographic studies. Although this analysis suffers from the vagaries of nonsimultaneous measurements and the use of different techniques to measure volumes, it is intended only as a means of estimating the utility of the RGV/EDV ratio in predicting the ventricular response to surgery. In Figure 1, the percent decrease in LV diastolic diameter measured within 7 to 10 days after aortic valve replacement is plotted against the ratio of RGV/EDV. The correlation coefficient of this relationship is 0.60.

As mentioned previously, the early postoperative echocardiographic measurements of LV size is remarkably predictive of the patients whose LV chamber will remain reduced in size and be accompanied by regression of hypertrophy. With the exception of 3 patients in Group A, all patients with an early postoperative reduction in end-diastolic diameter of less than 15% were in Group B. In addition, 16 of 18 Group A patients had a preoperative RGV/EDV ratio of greater than 0.25, whereas in 5 of 7 Group B patients the ratio was less than 0.25. Not unexpectedly, the mean EDVI of the Group B patients (180 ± 7 ml/m^2) was significantly greater ($p < 0.0001$) than that of Group A (129 ± 5 ml/m^2); all of the Group B patients had an EDVI >160 ml/m$_2$, whereas in only 2 of 18 in Group A was the EDVI >160 ml/m^2. The regurgitant stroke index, however, did not differ significantly in the 2 groups (39 ± 8 versus 37

* Because regurgitant volume = (regurgitant fraction) (total stroke volume) and total stroke volume = (systolic ejection fraction) (end-diastolic volume) by substitution, RGV/EDV = (systolic ejection fraction) (regurgitant fraction).

± 11 ml/m^2; p = not significant). The reduction in ventricular diameter observed after aortic valve replacement in patients with chronic AR has been reported to be 14 to 24% (average 20%).*[2,4,7,15,18–20,22–24] From the regression equation in Figure 1, this average value would correspond to a RGV/EDV ratio of 0.28.

The same information is presented in a different fashion in Figure 2. Using isopleths of regurgitant stroke index, the relationship between RGV/EDV and EDVI is illustrated to emphasize the hyperbolic relationship between the 2 values. By examining the coordinates of the Group A and Group B patients, one can see that with the exception of 1 Group B patient, a line drawn through the origin with a slope of 0.0014 m^2/ml clearly separates the 2 groups, and does so better than an EDVI of 160 ml/m^2. Thus, this analysis suggests that when the RGV/EDV ratio exceeds 0.0014 EDVI, a good ventricular response to surgery can be expected.

If, indeed, the premise is correct that the regurgitant stroke volume/end-diastolic volume ratio is the major determinant of the *ventricular* response to surgical correction of chronic AR, it follows that the partial functions of end-diastolic volume, regurgitant volume, total stroke volume, systolic ejection fraction, and regurgitant fraction should each be of some predictive value as well. The particular success of end-systolic volume as a means of predicting a good or bad outcome after aortic valve replacement[2–4,7–9] might be explained by the fact that end-systolic volume is directly related to end-diastolic volume and inversely related to total stroke volume, regurgitant volume, and ejection fraction. Thus, a large end-diastolic volume, a small total stroke volume or regurgitant volume, and a reduced ejection fraction would all tend to reduce the RGV/EDV ratio, result in a larger end-systolic volume, and presage a poorer ventricular response to valve replacement. In this regard, it is of interest that Boucher et al[20] found that among 20 patients with chronic AR, "the magnitude of the early postoperative decrease in end-diastolic volume correlated best with the decrease in (total) stroke volume (r = .92)."

If the major portion of the reduction in ventricular size after aortic valve replacement can be demonstrated immediately after surgery,[4,7,15,18–20] there is reason to believe that this volume change is primarily the consequence of elimination of the regurgitant volume and not to an improvement in ventricular function due to relief of the volume overload. Our success in predicting the ventricular response to surgery, therefore, lies in our ability to distinguish the volume overload itself from the chronic malefic effects of this hemodynamic burden on the ventricle.

Therefore, there are convincing conceptual reasons and some experimental data as well to indicate that the relative size of the regurgitant and end-diastolic volumes is the major determinant of the ventricular response to surgical correction of chronic AR. Whatever the explanation for the dilated myopathic ventricle in advanced chronic volume overload, it should be realized that any increase in end-diastolic volume over and above that directly attributed to the regurgitant volume will decrease the proportional volume change after valve replacement and does so in a nonlinear (hyperbolic) fashion.

Appreciation of this fact will not answer the question, "When should we operate on the patient with chronic AR?" However, we should be able to predict, if a patient is to undergo valve replacement, what the ventricular response will be. This information, in turn, will influence our decision regarding surgery. For example, in asymptomatic or minimally symptomatic patients with substantial AR, determination of when the product of systolic ejection fraction and regurgitant fraction begins to decrease may be sufficient reason to recommend valve replacement. The precision with which we can make these judgments will, of course, depend on our ability to assess accurately both systolic ejection fraction and regurgitant fraction in patients with chronic volume overload. The recent success of radionuclide angiography in the quantification of regurgitant fraction[25–29] may provide the necessary tools to test this hypothesis in a prospective study.

* Diameter change derived from echocardiographic measurement or decrease in cube root of angiographic volume.

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Current Status of Mitral Commissurotomy: Indications, Techniques, and Results

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Mitral commissurotomy was the first successful cardiac operation in the modern era, beginning with Bailey's report of closed commissurotomy in 1949. As the techniques of cardiopulmonary bypass improved and its risks decreased, the debate between proponents of open versus closed commissurotomy was largely resolved. Open commissurotomy is preferred in most Western countries because it decreases the risk of intraoperative embolism of dislodged thrombotic or calcific material, it allows repair of the subvalvular apparatus, and, as will be discussed further, it permits correction of mitral regurgitation without necessarily replacing the mitral valve. In the United States in particular, closed commissurotomy is rarely taught now, because one cannot entrust to a trainee the responsibility for a blind opening thrust as readily as one can delegate and guide an open commissurotomy. Thus, in the next generation of American surgeons, expertise with closed commissurotomy will be rare or nonexistent.

However, in the underdeveloped and developing countries where resources are limited, rheumatic heart disease is so prevalent, and mitral commissurotomy is performed often, open commissurotomy may be too costly and time-consuming. Similarly, closed commissurotomy is still used extensively in the United Kingdom, where the modern technique of transventricular dilation originated, and there are still many surgeons who are skilled in the technique.

Techniques of Operation

Open mitral commissurotomy is usually carried out through a median sternotomy incision with regular cardiopulmonary bypass techniques that include cannulation of the venae cavae through the right atrium for venous drainage and cannulation of the ascending aorta directly for return of oxygenated blood.[1] The aorta is clamped proximal to the aortic cannula to provide a quiet bloodless field and to prevent release of calcific or thrombotic material into the systemic circulation. Myocardial protection is usually provided by cold cardioplegic arrest. The left atrium is then approached from the right side and is opened posterior to the interatrial septum. Intraatrial clot is evacuated and the lines of commissural fusion are identified. The commissures are divided sharply almost to the anulus. When there is subvalvular fusion of the chordae, these may be incised down to the papillary muscles, and if necessary, the heads of the papillary muscles themselves may be divided to enhance mobility of the leaflets (Fig. 1). Surface calcification of the leaflets may be debrided, provided the underlying valve substance is relatively supple. A few surgeons use more elaborate reconstructive techniques, including correction of anular dilatation or deformity, as discussed herein. Uncorrectable shortening and fusion of the subvalvular apparatus or extensive calcification precludes successful commissurotomy and is an indication for valve replacement. After commissurotomy has been accomplished, the ventricle can be filled with blood or saline solution while the valve is observed directly to assess regurgitation. The left atrial appendage should be oversewn in the course of the operation to eliminate the major source of emboli.

Clearly, these assessments and techniques are not feasible with closed commissurotomy, which is usually carried out through a left thoracotomy. The left atrial appendage is opened through a pursestring suture and any thrombus is evacuated if possible. A dilator is inserted through the apex of the left ventricle, and the valve is opened progressively while its status is monitored by a finger inserted through the left atrial appendage.

Results of Operation

Early mortality: The hospital mortality for open commissurotomy in experienced hands is 1 to 2%. This low risk precludes statistical analysis of factors that increase operative risk, because most reports include between 100 and 200 patients and only 1 to 3 operative deaths. Vega et al[2] reported 2 deaths in 159 patients (1.2%); 1 death was due to "cardiorespiratory failure" and the other to preoperative cerebral embolism. In 1974 Mullin et al[3] reported 100 consecutive operations, with no deaths among 94 patients who had open com-

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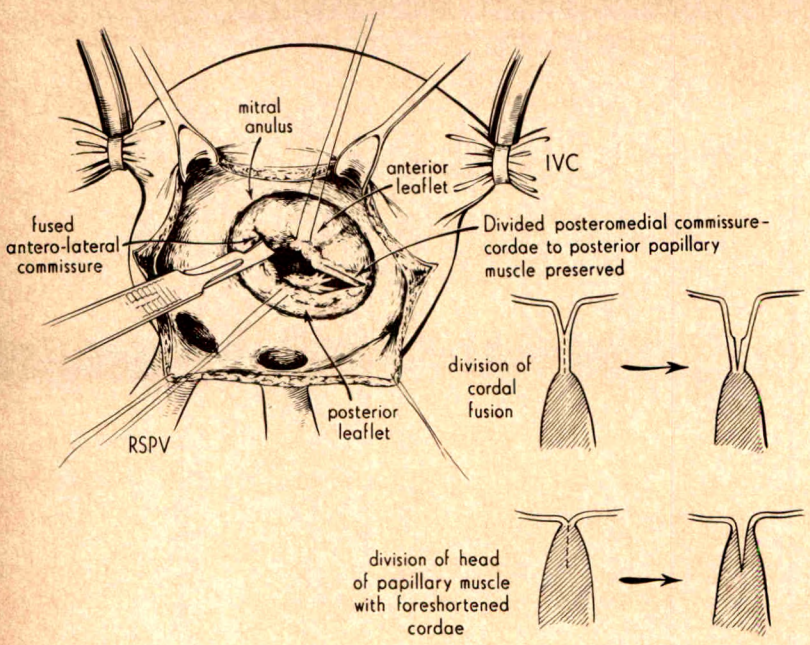

FIGURE 1. Upper left, the mitral valve at open commissurotomy as seen by the surgeon. The patient's head is to the left; the atrium has been opened anterior to the right pulmonary veins. The fused commissures are identified, and as each commissure is opened, the subvalvular structures are identified and preserved. **Lower right,** an aggressive surgical approach to valves with fused and shortened chordae. (Reproduced, with permission, from Bonchek LI and Brooks HL, eds, ref 1. IVC = inferior vena cava; RSPV = right superior pulmonary vein.

missurotomy alone or in combination with other valve operations, but 3 deaths from low cardiac output in 6 patients who had commissurotomy with coronary bypass. With current techniques of myocardial preservation, such deaths should be avoidable. Montoya et al[4] reported 2 deaths in 100 consecutive patients, 1 death due to delayed hemorrhage during a hypertensive crisis and 1 to infarction in a patient who underwent concomitant mammary artery implantation. Finally, we[5] reported 100 consecutive operations from the University of Oregon with 1 death due to hemorrhagic pancreatitis. Thus, associated coronary disease was implicated in 4 of the 8 deaths, but coronary disease is an uncommon finding in patients with mitral stenosis, who are usually women under the age of 50 years.

The reported mortality for closed commissurotomy has been somewhat higher, 3.7 to 7%, but the current mortality is probably lower. In a report[6] of 273 patients who underwent operation at the Massachusetts General Hospital between 1963 and 1968, hospital mortality was 3.7%, but there were no operative deaths in 140 consecutive patients operated on after 1970. Fraser et al,[7] in Glasgow, reported a hospital mortality rate of 4.2% in 359 patients operated on from 1957 to 1974, but there was only 1 operative death in the last 77 patients. This lower mortality rate is due not only to improved anesthesia, fluid and blood replacement, drug treatment of arrhythmias, mechanical ventilators, and the like, but also to improved selection of patients for closed commissurotomy. Now that the risks of cardiopulmonary bypass and mitral valve replacement are low, and good prosthetic devices are available, closed commissurotomy is restricted to the most suitable patients. Thus, current improved results with closed commissurotomy reflect experience with a highly selected and very favorable group of patients who would also undoubtedly do extremely well with open commissurotomy.

Long-Term Results

Mortality: Late deaths after isolated mitral commissurotomy are uncommon, as patients in whom recurrent symptoms develop should undergo repeat operation (usually valve replacement; see below), and this should be accomplished with minimal mortality. We[5] reported 1 late death from metastatic breast cancer in 96 operative survivors (3 were lost to follow-up) during a follow-up period that extended to 136 months (mean 46 months). Sixteen patients underwent reoperation with no deaths; 15 had valve replacement and 1 had repeat commissurotomy. In the report of 100 patients by Montoya et al,[4] there was also only 1 late death in an average follow-up period of 51 months. The patient who died had undergone aortocoronary bypass 6 months after commissurotomy, and he died suddenly 3.5 years later, presumably of acute infarction. Mullin et al[3] likewise reported 1 death in 97 survivors of the initial operation. This patient died after tricuspid valve replacement performed 5 months after mitral commissurotomy and tricuspid anuloplasty.

Functional results of operation: Overall, functional results are excellent after open commissurotomy, with 95% of the patients returning to New York Heart Association functional class I or II initially.[5] The late functional results of mitral commissurotomy are affected by 5 major phenomena: (1) left ventricular dysfunction; (2) pulmonary vascular disease, right ventricular failure, or tricuspid regurgitation, or a combination of the 3; (3) systemic emboli; (4) other coexistent cardiac disorders such as coronary artery or aortic valve disease; and (5) residual or progressive mitral valve disease.

Left ventricular dysfunction: In mitral stenosis, unlike other cardiac valve disorders, there is no increase in the pressure or volume load of the left ventricle, and serious left ventricular abnormalities are uncommon.

Nonetheless, Feigenbaum et al[8] documented decreased left ventricular compliance in 19 of 32 patients with pure mitral stenosis. They suggested that obstruction to left ventricular filling might cause "ventricular atrophy," which could explain why improvement in cardiac output often progresses for several months after commissurotomy. However, the apparent decrease in ventricular compliance may have been due to the inevitable shortening of the mitral subvalvular apparatus, which tethers the wall of the ventricle to the valve anulus and restricts diastolic filling of the ventricle. Such studies would have been more persuasive if they had also been performed serially postoperatively in patients with mitral stenosis who underwent mitral valve replacement with excision of the mitral valve and the subvalvular apparatus. In that regard, we have observed decreased compliance of the left ventricle intraoperatively even after valve replacement, and find that at the conclusion of cardiopulmonary bypass left ventricular filling pressure (mean left atrial pressure) can often increase rapidly with transfusion of small increments of blood from the pump-oxygenator. Presumably, this abnormality of compliance is either reversible or hemodynamically unimportant in the long term, because it has not been noted in any large series of patients as a cause of recurrent symptoms after commissurotomy.

On the other hand, substantial depression of left ventricular contractility is found occasionally. Such primary ventricular dysfunction is probably due to previous rheumatic carditis, but might result instead from unrelated cardiomyopathies such as those due to excessive alcohol ingestion or previous viral infection. Because the severity of left ventricular dysfunction in mitral stenosis does not correlate with the duration or severity of the mitral valve disease, early operation cannot be justified to prevent deterioration of left ventricular function. Rather, as will be discussed further, the primary reasons for recommending early commissurotomy are loss of exercise capacity, the high preoperative risk of major systemic emboli, the possibility that the valve will be more pliable if repaired early, and the need to prevent irreversible pulmonary damage.

Pulmonary vascular disease and related abnormalities: The pulmonary hypertension in patients with mitral stenosis has 3 components: (1) the direct hydraulic consequence of obstruction to left atrial emptying, (2) reactive pulmonary vasoconstriction, and (3) interstitial pulmonary fibrosis with mechanical compression of the pulmonary vessels.

Several investigators[9,10] have demonstrated that the decline in pulmonary artery pressure after commissurotomy is due not only to relief of the physical obstruction, which obviously occurs immediately, but also to regression of a vasoconstrictive component of pulmonary vascular resistance. Nonetheless, many patients retain mild-to-moderate pulmonary hypertension despite successful commissurotomy, which suggests that some element of vasoconstriction often persists, or that there is irreversible interstitial fibrosis, or both.

Therefore, it is essential to offer operation before there is irreversible damage to the pulmonary vasculature and right ventricle. The need for concomitant tricuspid valve repair or replacement increases the risk of commissurotomy considerably, but the exact risk is difficult to determine, because combined operations are excluded from most reports of open commissurotomy and, obviously, from all reports of closed commissurotomy. Although tricuspid regurgitation is usually secondary to pulmonary hypertension, tricuspid stenosis can result from rheumatic valvulitis. Reconstructive techniques should be used and valve replacement should be avoided, because mechanical valves in the tricuspid position are prone to thrombosis, and tissue valves have uncertain durability in these patients, who are often young.

Systemic emboli: Prevention of systemic emboli is one of the most important and unequivocal benefits of commissurotomy. In our report of 100 patients,[5] 13 had preoperative emboli and only 2 had postoperative emboli. Furthermore, *sinus rhythm did not provide adequate protection from preoperative emboli*, because 6 of the 67 patients (9%) in sinus rhythm had emboli preoperatively. The risk of emboli was higher in patients with atrial fibrillation, however, and 7 of 32 (21%) had emboli preoperatively. Of the 2 patients with emboli postoperatively, 1 had sinus rhythm and the other had atrial fibrillation. Importantly, we found no correlation between the incidence of embolism and the presence of left atrial thrombus at operation; Mullin et al[3] and Montoya et al[4] found likewise. In contrast, Vega et al[2] found a significant positive correlation in that 27% of their patients with a history of emboli had left atrial thrombi, whereas only 8% of patients without a history of embolism had atrial thrombi. Postoperative emboli were also uncommon in these other reports (Vega, 2%; Montoya, 4%; Mullin, 4%). In our patients, long-term anticoagulation was restricted to older patients with atrial fibrillation, but its use in the other studies was not defined.

Coexistent cardiac disorders: As already noted, coronary artery disease was directly implicated in 4 of the 8 deaths in the reports cited, which dated from the early years of coronary bypass. The number of coronary deaths should be much lower now, because coronary bypass is regularly combined safely with valve procedures that are much more complex than mitral commissurotomy. In general, coexisting disease of the coronary arteries or of other heart valves usually overshadows the need for mitral commissurotomy, and the severity of these other cardiac problems usually determines late survival.

Residual or progressive mitral valve disease: Late deterioration after mitral commissurotomy may be due to *restenosis* of the mitral valve, to residual (unrelieved) mitral stenosis, or to mitral regurgitation induced at operation. The latter is usually apparent immediately, and in the majority of patients with severe iatrogenic regurgitation, the proposed commissurotomy is converted to mitral valve replacement. The incidence of this conversion is infrequently reported and is therefore difficult to assess. We did not assess the issue directly in our report. Montoya et al[4] found replacement necessary in 28% of patients in whom open commissurot-

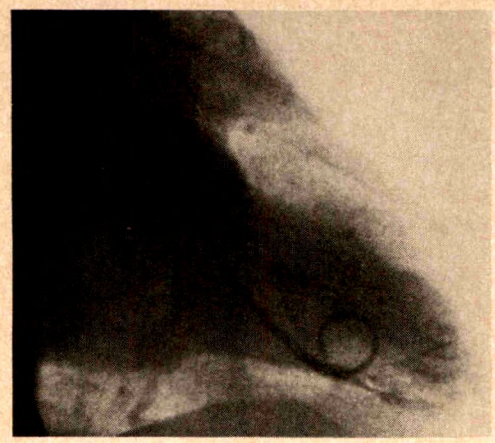

FIGURE 2. Preoperative left ventriculogram in the right anterior oblique projection. Massive mitral regurgitation is apparent.

FIGURE 3. Postoperative left ventriculogram. Mitral regurgitation has been abolished. The Carpentier ring is visible at the mitral anulus, but there is no other prosthetic material and the patient's native valve is intact.

omy had been planned. Grantham et al[6] carried out mitral valve replacement in 20 of 273 patients (8%) undergoing closed commissurotomy.

The need for valve replacement may be decreased considerably by reconstructive techniques to correct mitral regurgitation. Figure 2 displays the preoperative ventriculogram in a patient of mine with severe nonrheumatic mitral regurgitation. A postoperative ventriculogram (Fig. 3) indicates complete correction of the regurgitation without valve replacement. Correction was accomplished using Carpentier's techniques by excision of a portion of 1 leaflet of the mitral valve, shortening of elongated chordae, and correction of anular dilatation by insertion of a cloth-covered, rigid Carpentier ring. Although these techniques are rarely necessary in patients who undergo commissurotomy for pure mitral stenosis, we use them regularly in patients with mitral regurgitation.[11] The techniques of mitral valve reconstruction developed by Carpentier et al[12] can markedly decrease the need for mitral valve replacement in patients with mitral regurgitation.

There is still considerable controversy about the frequency of recurrent stenosis. Only 2 studies provide adequate hemodynamic documentation of restenosis after closed commissurotomy. Such proof requires preoperative hemodynamic assessment of the severity of stenosis, a postoperative study that documents relief of the stenosis, and a later hemodynamic study that demonstrates recurrent stenosis. Higgs et al[13] at the National Institutes of Health found that of 163 patients who underwent mitral commissurotomy and had preoperative and early postoperative catheterization, 45 required late recatheterization for recurrent symptoms. Of these 45 patients, only 5 had recurrent stenosis after initially successful commissurotomy. Sixteen other patients had residual, unrelieved stenosis, 15 had residual stenosis and operatively induced mitral regurgitation, and 99 had other cardiac disorders. Lyons et al[10] reported similar findings on the basis of sequential hemodynamic studies. Thus, restenosis can occur after closed commissurotomy, but it is uncommon in the hands of experienced surgeons. Although the reported incidence of reoperation for restenosis after closed commissurotomy ranges from 3 to 9%, many, if not most, of these operations are undoubtedly necessitated by residual stenosis.

The incidence of restenosis after open commissurotomy is not as easy to assess because the procedure is newer and follow-up is shorter. Reoperation for restenosis was necessary in only 2 of 159 patients followed up by Vega et al[2] (0.4% per patient-year), but the average follow-up was only 3 years. In Montoya's series[4] of 105 patients followed up an average of 51 months, 1 patient had a second open commissurotomy and 2 had valve replacement. Our own study[5] of 100 patients followed up an average of 46 months provided an actuarial analysis of the incidence of late reoperation. Overall, 16 of 99 survivors required reoperation, with an actuarial incidence of 9% at 5 years. The incidence increased thereafter, but the number of patients at risk was too small to permit statistical analysis. We observed a higher incidence of reoperation than Montoya, but the experiences are not comparable. All of their first operations were performed after 1970, when good prosthetic valves were available and were used often. Twenty-eight percent of their patients scheduled for commissurotomy underwent valve replacement. In contrast, our series of patients began in 1960, when prostheses were just being developed. Almost all patients who required reoperation were first operated on before 1970, when prostheses were less desirable than they are now and imperfect native valves were more often preserved. Our study revealed a distinct relation between leaflet deformity and the need for reoperation. Of 77 patients with only fair or poor leaflet anatomy, 17 and 23%, respectively, had undergone reoperation at the time of the study, whereas none of the 10 patients with good leaflet anatomy had done so. Thus, the true incidence of late reoperation after commissurotomy with current techniques and criteria for selection of patients is not clearly defined.

Conclusions

The operative mortality for open commissurotomy alone in experienced hands is ≤1%. Functional results are initially excellent in approximately 95% of patients, and postoperative emboli are rare. Nonsurgical therapy imposes substantial risks of embolism (18% preoperatively in the series of Montoya et al[4] and 13% in our report). Because emboli and left atrial thrombi frequently occur in patients with sinus rhythm, it is difficult to decide which patients should receive chronic anticoagulant therapy preoperatively. Long-term preoperative anticoagulant therapy poses notable risks, with a 5-year mortality that exceeds the combined surgical and late mortality of commissurotomy.

Avoiding all of the risks cited (including tricuspid regurgitation and irreversible pulmonary hypertension) and restoring functional capacity may be well worth the minimal surgical risk to most patients. Open mitral commissurotomy can reasonably be offered to patients with mitral stenosis who wish to function in New York Heart Association class I but are unable to do so. This means that operation should be offered when cardiac symptoms cause curtailment of normal daily activities and should not be withheld until the patient is incapacitated. In addition, a patient who sustains a major systemic embolus should have cardiac catheterization. If hemodynamically significant mitral stenosis is found, the risk of an operation is much less than the risk of another major embolus or chronic systemic anticoagulation. With current diagnostic techniques, including echocardiography, the likelihood of successful commissurotomy can be predicted with reasonable confidence. Obviously, the cardiac surgeon must be experienced in reconstructive mitral surgery, not just in valve replacement. If, in a particular patient, there is uncertainty that the valve will be suitable for commissurotomy, the indications for valve replacement I have discussed elsewhere[14] should be applied, because they are less liberal.

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Atrioventricular Nodal Rhythm Reconsidered

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For over 50 years after Tawara's description of the atrioventricular (A-V) node,[1] clinicians and scientists referred to pacemaker activity from that region as A-V nodal or simply nodal. In the mid-1960s, there was a rapid movement toward the use of the term A-V junctional rather than nodal. We believe that the basis for this change was inadequate on both clinical and electrophysiologic grounds, and that the continued use of "junctional" maintains an unnecessary ambiguity. We review here the literature for the original change, and conclude with the grounds for clinical separation of low atrial from A-V nodal pacemakers.

The initial argument against nodal rhythm was based on cellular studies by Hoffman and Cranefield.[2] In 1964, they criticized the use of "so-called nodal beats," because, "In our opinion, there are no automatic fibers in atrioventricular node, although there may be a few at the junction of the lower node with the bundle of His." They particularly objected to the designation "upper nodal rhythms," suggesting that these rhythms actually originate in the atrial tissue of the coronary sinus region.

The first clinical study substituting junctional for nodal rhythm was by Kistin in 1966,[3] without explanation. Scherf made the substitution "official" in an editorial in this journal in 1967,[4] explaining that the uncertainty of automaticity required the change, but only as a temporary expedient pending further studies. Pick and Langendorf in 1968[5] joined in the call for junctional to replace nodal for impulse generation, citing the failure to demonstrate automaticity and added clinical objections. Quoting them directly, "relationships of retrograde P waves to QRS are not only dependent on the proximity of the ectopic pacemaker to atria or ventricles but also on the relative speed of conduction in either direction." The supporting citations were clinical deductions based on surface electrocardiograms. As stated, it is unarguable; that the statement required a change in nomenclature *is* arguable. Pick and Langendorf[5] added a third objection; citing an animal study,[6] "experimentally proved retrograde atrial activation may produce, against the rule, upright P waves in Leads II, III, and aVF." However, this study by Moore et al[6] reported an R-P interval for the retrograde atrial activation of 110 ms, in contrast to a P-R of 100 ms for beats originating in the low right atrium, and a P-R of 110 ms for sinus beats. Pacing the coronary sinus region in human subjects[7] produced inverted P waves in II, III, and aVF, and the P-R interval was only minimally shortened, as Moore had found in the dog.[6]

In 1973, Hecht and Kossman[8] and a group of 8 prestigious cardiologists also recommended replacing "A-V nodal" with "A-V junctional," citing similar reasoning, based on 2 electrophysiologic studies.[9,10] These 2 citations also raised questions about P-wave morphology, but were unambiguous about the sequence of P and QRS in relation to the origin of beats. In the first study in human subjects, junctional beats conducted retrogradely produced diphasic P waves buried in the QRS.[9] Moore et al[10] again reported that atrial beats had P-R intervals, whereas ventricular pacing with retrograde atrial activation produced R-P intervals, without exception.

There is then ample experimental evidence that coronary sinus or low atrial pacemakers have slightly shortened P-R intervals, but retrograde atrial activation produces R-P intervals,[6,10] or at worst simultaneous P and QRS complexes.[9] This is based on a principle that has been repeatedly proved, that the slowest conduction in the entire heart is found in the transitional zone between the atrium and node.[11–13] The most precise correlation between morphology and electrophysiology, using 3-dimensional reconstruction techniques, was reported from Amsterdam in 1974[14]; they found that

TABLE I Values for Atrioventricular Conduction

From His bundle recordings in human subjects,[8] in milliseconds:	
P-R interval = P-H + H-R = 162 ms	
P-H = 119 ms	
H-R = 43 ms	
P-H interval = P-A + A-H = 119 ms	
P-A = 27 ms	
A-H = 92 ms	
From combined morphologic and electrophysiologic[14] study of atrioventricular node, in percent of A-H interval:	
Atrial to atrionodal (AN) region	20%
Activation time for AN region	60%
AN to His bundle	20%
A-H interval	100%

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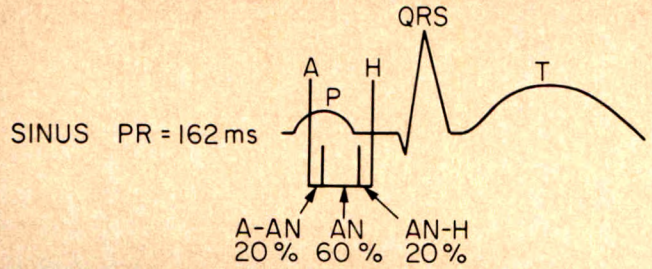

FIGURE 1. A graph indicating temporal relationships of the surface electrocardiogram and His bundle electrogram values,[8] specified in Table I. Below the isoelectric line are percentages of the A-H interval that were found in a combined morphologic and electrophysiologic study.[14] For the drawing, a P-wave duration of 90 ms was assumed, and a QRS duration of 80 ms. The regions of the A-V node (AN, N, and NH) are defined in the text. RA = right atrium.

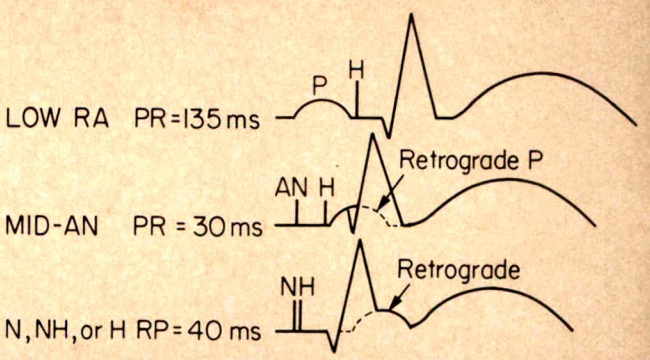

FIGURE 2. Graphic presentation of the P and QRS sequences for ectopic impulse formation. The **top** sequence represents an ectopic impulse beginning in the low right atrium (RA). The **middle** graph represents the sequence for an impulse originating in the mid-point of transitional cells (AN); 30% of the A-H interval would be consumed in anterograde and retrograde conduction, respectively, resulting in a P wave nearly coincident with the QRS and a P-R interval of 30 ms, compared with a sinus beat with a P-R of 162 ms and a low atrial origin with P-R of 135 ms. A beat originating in the N, NH, or H regions would be separated by only a few milliseconds, and all would result in a P wave following the QRS and an R-P interval of 40 ms. (The P wave was deliberately drawn in the upright position, although we believe that the vector will be changed in most cases of ectopic pacemaker, to emphasize the importance of interval and sequence over P morphology).

80% of the atrial-His interval was consumed between the atrial and transitional zone (AN cells) (Fig. 1).

Using the average intervals provided by Hecht and Kossmann[8] from human His bundle recordings, and the subdivisions of the A-H interval observed by Anderson et al,[14] Figure 2 illustrates the P-QRS relationships expected from impulses originating in the low right atrium, midway in the transitional zone (AN), and in the node (N), NH region, or even the His bundle. (The intervals between these last 3 are so short that they are lumped.) The results are in keeping with the observed P-R and R-P intervals reported earlier.[6,7,9,10]

In rereading the original criticisms on A-V nodal terminology,[2,5,8] they shared a substantive objection to the subdivision of nodal into upper, middle, and lower A-V node on the basis of surface electrocardiograms. On the basis of cellular studies from many centers, we agree that it would be impractical, if not impossible, to identify the site of origin within the node by clinical means. This does not invalidate the original term A-V nodal, nor does it invalidate the clinical separation of nodal from atrial pacemaker activity. There is, in fact, nearly unanimous agreement[11–14] that the great majority of conduction delay between atrium and ventricle or between ventricle and atrium occurs in the transitional zone (AN cells) between the 2, permitting easy separation of low atrial pacemakers from nodal on the simple basis of initial occurrence of a P or a QRS complex. The term junctional unnecessarily obscures that important clinical distinction.

To return to the first objection to nodal rhythm, automaticity,[2] Watanabe and Dreifus[15] in 1968 reported that the great majority of spontaneous A-V junctional rhythms arose from the NH region. And finally, Wit and Cranefield[16] provided a welcome release from 15 years of uncertainty; they found automaticity in mid-nodal (N) cells by experimentally uncoupling the A-V node from the atrium.

In summary, the term junctional makes no improvement in the understanding of the origin of ectopic rhythms over the earlier, historic term, A-V nodal. Because A-V junctional is now used to include low atrial pacemakers that can be separated clinically by the presence of a measurable P-R, that term is more ambiguous than the current state of our knowledge requires. We urge the abandonment of that term, and the restoration of A-V nodal, without clinical subdivision, as the preferred term for automatic rhythms from the A-V node.

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The AJC in August 1958

CAROLE A. WARNES, MB, BS, MRCP and WILLIAM C. ROBERTS, MD

Hemodynamics of Mitral Regurgitation (Julio C. Davila)

This report, part of the symposium on mitral regurgitation (MR), describes hemodynamic features of MR and physiologic sequelae of surgical reduction of mitral anular size. Of 128 patients with significant MR, with or without mitral stenosis, all had right-sided cardiac catheterization, and 22 had left atrial puncture. Of 58 patients operated on, 56 had hemodynamic studies performed at surgery, before and after either partial or complete elimination of MR. The left-sided pressure changes of MR were documented at operation before and after mitral valve manipulation. The hemodynamic derangements usually reverted to normal. The left ventricular (LV) end-diastolic pressure and total LV volume, however, sometimes failed to revert to normal, and often these patients died despite apparent diminution or elimination of MR by operation. The author emphasized that patients with long-standing severe MR may not be benefited by the operation because when LV dilatation, the major compensation of MR, is severe, correction of MR actually may aggravate myocardial dysfunction by abolishing the "escape exit" into the low pressure left atrium and thus may increase LV work. He concluded that operative candidates should be selected before irreversible damage to LV myocardium had occurred. This report introduced important concepts of surgical treatment of MR, and is a fine example of physiologic orientation of early surgeons of valvular heart disease.

Modern Concepts of Hypertension and Its Treatment (Joseph H. Hafkenschiel, Edward Weiss, William Likoff, John K. Clark, and Charles C. Wolferth)

This 19-page article reports a conference on systemic hypertension (SH) at Lankenau Hospital, Philadelphia. SH was considered to have 3 major causes: hereditary, renal, and psychogenic. This latter concept was given considerable emphasis, and the "personality inside an individual" was considered etiologically important in most patients. A study of 130 patients with SH who were followed up for >5 years was reported: Only 66% survived for 5 years. Adrenalectomy for refractory SH was still considered acceptable therapy, but the conference invoked considerable dispute regarding the necessity, if any, for medical treatment for less severe forms of SH. Weiss stated, "In the so-called malignant SH, it has been demonstrated that ganglionic blockers prolong the life of these patients. Beyond that I have not seen any adequate demonstration that the drug treatment of SH prolongs life or changes the course of the vascular disease." Medical therapy consisted essentially of rauwolfia and hydralazine. The results of chlorothiazide, then a new drug, were considered impressive. Some clinicians, however, remained convinced that drug therapy was used too early and objected to the use of potent drugs in the treatment of early or mild SH.

This conference reflects the paucity of scientific data then available on SH. No definition of SH was given. In the last 25 years, the importance of treating SH has become obvious, and treatment has become more vigorous and introduced at earlier stages. However, recent observations on *mild* SH treated with thiazide diuretic drugs suggest a reconsideration of this approach.

Ebstein's Anomaly (Joseph B. Vacca, Donald W. Bussman, and J. Gerard Mudd)

This report describes 3 cases of Ebstein's anomaly, and reviews the data on 105 cases previously reported on since Ebstein's original description in 1866: 55 were diagnosed clinically and 53 at necropsy. The typical clinical, radiographic, and electrocardiographic findings were described, and the frequent association of atrial septal defect and rhythm abnormalities was noted. Cardiac catheterization was considered helpful and diagnostic, but was acknowledged to be hazardous and possibly dangerous in patients with this anomaly. Diagnosis of Ebstein's anomaly now is obviously much easier because of echocardiography with or without use of the intracavitary electrode. Despite the improved diagnostic accuracy and more successful treatment of rhythm abnormalities, however, surgical treatment remains less than ideal, and the overall survival has probably improved only slightly in the last 25 years.

Pulmonary Atresia With Ventricular Septal Defect and Aortic Regurgitation: Diagnosis by Echocardiography With Diastolic Vibration of Both Right and Left Sides of the Ventricular Septum

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CHARLES E. BEMIS, MD
E. ELAINE GLAZIER-LASKEY

High-frequency[1] diastolic fluttering of the left side of the ventricular septum has been reported with aortic regurgitation (AR)[1] and of the right side of the ventricular septum with a ruptured aneurysm of the sinus of Valsalva.[2] This report describes the echocardiographic features of a patient with pulmonary atresia and ventricular septal defect (VSD) with AR.

A 26-year-old man with cyanotic congenital heart disease was admitted for precise diagnosis. Blood pressure was 120/60 mm Hg. The peripheral pulses were collapsing. Auscultation revealed a single accentuated second sound, a grade 3/6 decrescendo blowing diastolic murmur along the left sternal border, and a presystolic murmur and short, early grade 2/6 ejection murmur at the apex. The electrocardiogram demonstrated right atrial and biventricular enlargement. Chest X-ray revealed right ventricular enlargement and a right aortic arch with an absent pulmonary trunk and evidence of bronchial collateral circulation. M-mode and 2-dimensional echocardiography demonstrated aortic overriding of the ventricular septum, a large VSD, and marked right ventricular hypertrophy, and these findings were confirmed by catheterization. The left ventricle was enlarged and the pulmonary valve was not visualized. The aortic valve cusps were thickened. On M-mode echocardiography, diastolic high-frequency fluttering of the mitral valve as well as both sides of the ventricular septum was recorded (Fig. 1). At catheterization the pulmonary arteries were opacified by bronchial collateral vessels when contrast material was injected into the descending aorta. Significant (3+ to 4+) AR was noted.

The role of echocardiography in the diagnosis of conotruncal abnormalities is well defined.[3,4] Incompetence of the systemic arterial trunk in these disorders is present in approximately 20% of patients.[4] However, the characteristic regurgitant murmur may be absent in 25% of these patients.[5] The finding of diastolic fluttering of the mitral valve and fluttering of both sides of the ventricular septum in the present case suggested incompetence of the systemic arterial trunk. The diastolic vibrations are presumably due to the effect of the valvular regurgitant jet striking the septum. In 62 patients with aortic overriding, Assad Morrell et al[3] noted fluttering of the mitral and tricuspid valves in 7 and 5 cases,

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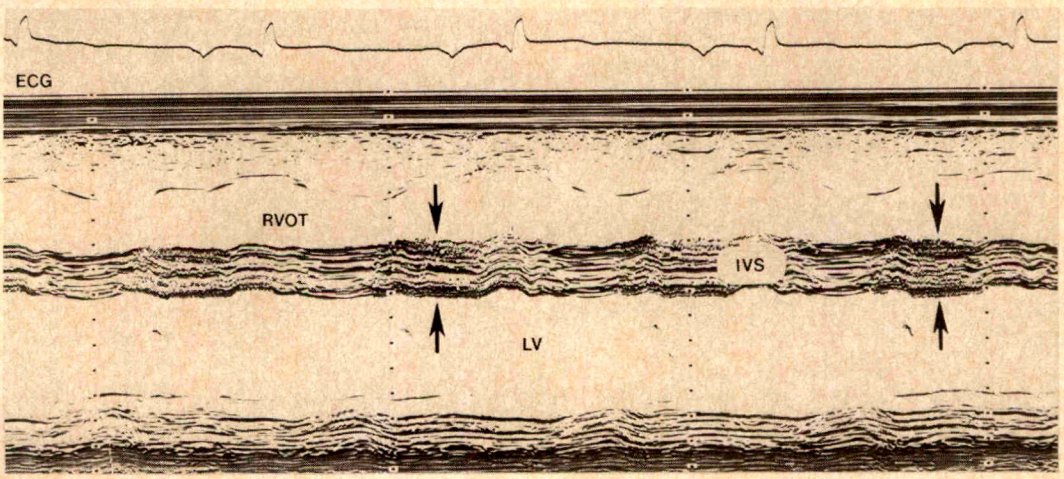

FIGURE 1. M-mode echocardiogram of the left ventricle (LV) below the level of the mitral valve. Fluttering of both sides of the interventricular septum (IVS) is noted (**arrows**). The right ventricular wall measures 13 mm in thickness. RVOT = right ventricular outflow tract.

respectively, in patients with truncal incompetence. If fluttering of both atrioventricular valves or both sides of the ventricular septum is recorded, aortic override should be suspected even though it may not be demonstrated by M-mode echocardiography.

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Real-Time 2-Dimensional Echocardiographic Imaging of Right-Sided Cardiac Vegetations in Ventricular Septal Defect

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Echocardiography is a valuable bedside technique for detecting cardiac vegetations in patients with infective endocarditis.[1] However, most reports concern left-sided cardiac structures, and few reports describe vegetations on the tricuspid or pulmonic valves[2–5] or in the right ventricle.[6,7] This report presents 2-dimensional (2-D) echocardiographic findings in 2 patients with ventricular septal defect (VSD) complicated by ventricular endocardial or pulmonic valvular alpha Streptococcus endocarditis with severe congestive heart failure.

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Patient 1 (24-year-old man): *The 2-D echocardiogram showed a defect high in the ventricular septum (Fig. 1). Attached to the right side of the septum around and above the defect were large mobile vegetations (15 × 25 mm). The vegetations projected into the right ventricular outflow tract during systole (Fig. 1, left) and closed the VSD during diastole (Fig. 1, right). Movement of the vegetations in systole and diastole was probably related to the left-to-right shunt. The left ventricle and left atrium were not enlarged and the left ventricle contracted well. There was no apparent attachment of the vegetations to the tricuspid or pulmonic valves, which were normal in structure and function. After 6 weeks of appropriate medical treatment, the diagnosis was confirmed by cardiac catheterization and operation, at which a 1 cm VSD was closed in the infundibular septum 2 cm below the pulmonic valve. At operation, there were no large vegetations, but some fibrosed thickening on the rim of the defect. The absence of vegetations at surgery may be the result of successful antibiotic treatment, but part of the vegetations embolized to the lungs during the period of medical treatment. The postoperative course was uneventful.*

Patient 2 (11-year-old girl): *Two-dimensional echocardiography showed a large high VSD in the region of the membranous septum (Fig. 2). Large vegetations were seen on the pulmonic valve, and pulmonic cuspal tissue fluttered chaotically in the right ventricular outflow tract and pulmonary trunk, indicating a torn pulmonic cusp. The patient received 6 weeks of medical therapy and had marked clinical improvement.*

In both patients, 2-D echocardiography confirmed the clinical diagnosis of VSD and infective endocarditis, with accurate delineation of the size and site of the large right-sided cardiac vegetations. The high quality of the pictures was partly related to the newer image-processing techniques, but also to the physique of the pa-

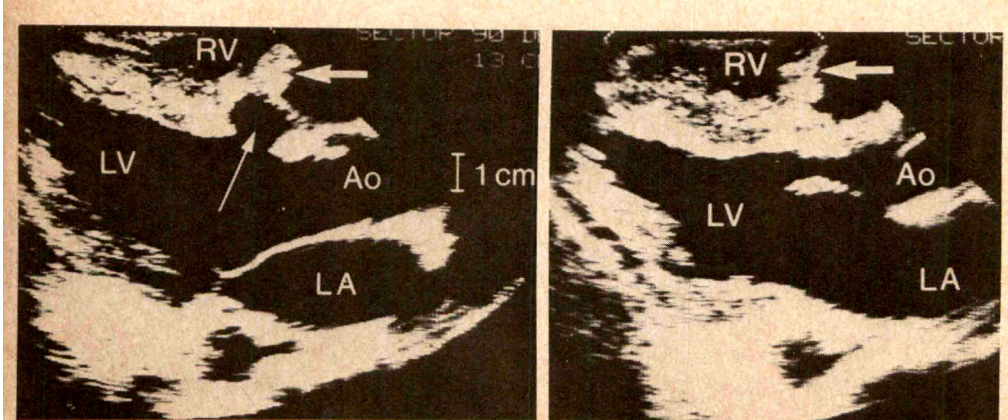

FIGURE 1. Left, echocardiogram (parasternal long-axis view, systolic frame), showing the defect in the interventricular septum (**fine arrow**) and large pedunculated vegetations (**heavy arrow**) in the right ventricular (RV) outflow tract. **Right,** diastolic frame. The defect has been closed by part of the vegetations (**heavy arrow**). Ao = aortic root; LA = left atrium; LV = left ventricle.

tients, to careful attention to echo-recording technique and to the use of appropriate echocardiographic views to demonstrate the right-sided cardiac chambers and valves. The subcostal and apical views were particularly useful in visualizing the tricuspid and pulmonic valves, the right ventricle, and its inflow and outflow tracts.

The clinical implication of large vegetations on left-sided cardiac structures has been recognized: (1) Valve destruction is usually severe, so that there is a high likelihood of the need for early or urgent operation, whereas (2) major systemic emboli occur in ≤30% of patients.[1] These 2 patients behaved in a similar manner, with severe destruction of the pulmonic valve in 1 and recurrent pulmonary emboli in the other. The hemodynamic lesions, however, were tolerated well and emboli, although important, were less crucial.

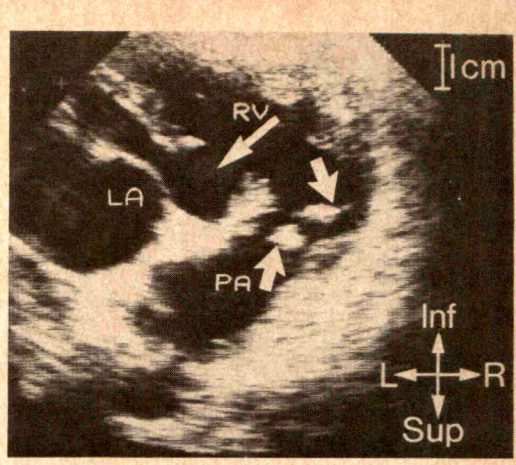

FIGURE 2. Echocardiogram (subcostal view) in the long axis of the right ventricular outflow tract, showing the ventricular septal defect (**long arrow**) in the high interventricular septum and large vegetations (**heavy short arrows**) on the pulmonic valve. LA = left atrium; PA = pulmonary artery; RV = right ventricle.

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Idiopathic Restrictive Cardiomyopathy: Differences of Left Ventricular Relaxation and Diastolic Wave Forms from Constrictive Pericarditis

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It has been frequently emphasized that the clinical features and hemodynamic characteristics of restrictive cardiomyopathy are similar to those of constrictive pericarditis.[1–3] Early diastolic dip and subsequent plateau pattern of the diastolic ventricular pressure curve (square root sign) have been considered to be characteristic in these diseases.[1,3] Left ventricular (LV) pressure was recorded with a tip manometer system in 3 patients with restrictive cardiomyopathy and constrictive pericarditis. This report describes the differences of LV relaxation and diastolic wave forms of these 2 diseases.

Among 263 patients who underwent diagnostic cardiac catheterization between January 1980 and December 1981, 3 had idiopathic restrictive cardiomyopathy and constrictive pericarditis. The diagnostic criteria of idiopathic restrictive

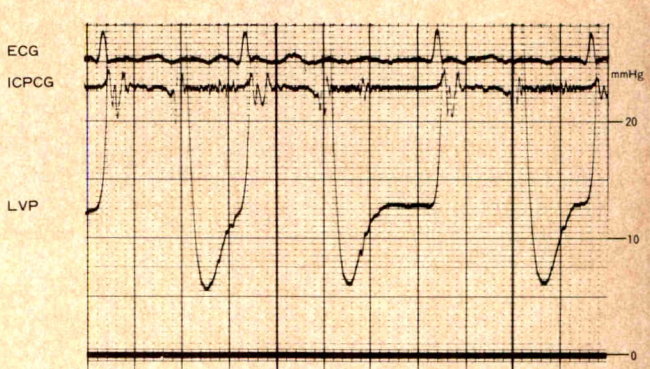

FIGURE 1. A high-gain left ventricular pressure (LVP) of constrictive pericarditis (Patient 2). The pressure was recorded with a Mikro-tip® angiocatheter with the simultaneous recordings of intracardiac phonocardiogram (ICPCG) and electrocardiogram (ECG). A typical square root sign was present.

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TABLE I **Left Ventricular Volume and Indexes of Contractility and Relaxation in Patients with Restrictive Cardiomyopath and Constrictive Pericarditis**

Patient	EDVI (ml/m^2)	EF (%)	peak (+)dP/dt (mm Hg/s)	peak (−)dP/dt (mm Hg/s)	peak (+)dp/dt / peak (−)dP/dt	(r
Restrictive Cardiomyopathy						
1	69	53	1,434	969	1.48	
2	73	63	1,480	680	2.18	1
3	82	76	1,410	590	2.39	1
Constrictive Pericarditis						
1	59	66	1,065	1,410	0.76	
2	54	61	1,500	2,062	0.73	
3	54	49	1,328	1,426	0.93	
Normal value (n = 22, M ± SD)	69 ±20	65 ±7	1,681 ±413	1,923 ±440	0.90 ±0.15	

Normal values are based on 22 patients without significant heart disease.[4,5]
EDVI = end-diastolic volume index; EF = ejection fraction; M = mean; peak (+) and (−)dP/dt = peak rate of left ventricular pressure inc and decrease; SD = standard deviation; T = the time constant of left ventricular pressure decrease.

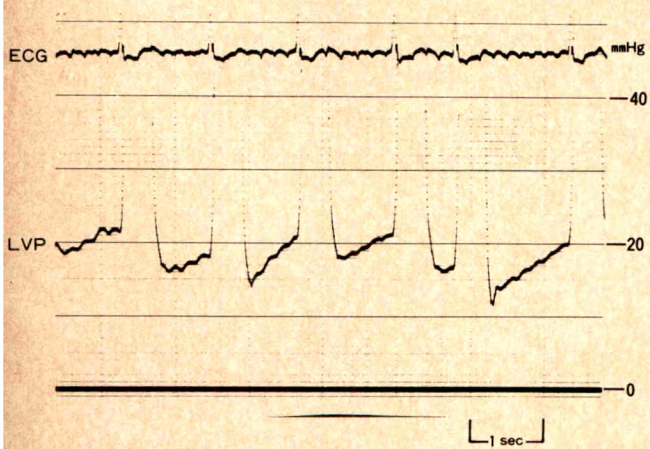

FIGURE 2. A high-gain left ventricular pressure (LVP) tracing of restrictive cardiomyopathy (Patient 3). Early diastolic dip and square root sign were absent even with the elevation of diastolic pressure and slow heart rate.

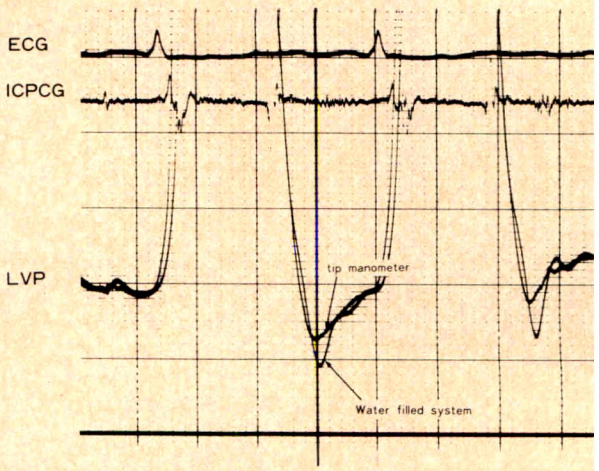

FIGURE 3. Simultaneous left ventricular pressure (LVP) recordings a tip manometer system and a fluid-filled system in restrictive ca myopathy (Patient 1). Early diastolic dip and square root sign were only in the tracing obtained with a fluid (water)-filled system. phenomenon was probably due to the exaggeration of the wave by the artifact of a fluid-filled system.

cardiomyopathy were (1) normal LV volume and ejection fraction, (2) evidence of stiff ventricle, (3) absence of severe LV hypertrophy, (4) absence of hypertrophic cardiomyopathy, (5) histologic findings consistent with stiff ventricle, and (6) unidentifiable cause of heart disease.

Precise descriptions of the catheterization procedures and data processing have been published elsewhere.[4,5] *Right ventricular (RV) pressure was recorded with a fluid-filled system, and LV pressure was recorded with a tip manometer system (Millar Instruments). RV or LV endomyocardial biopsy or both was performed in all cases of restrictive cardiomyopathy. One patient with restrictive cardiomyopathy and 3 patients with constrictive pericarditis underwent pericardiectomy.*

Both RV and LV end-diastolic pressures were elevated in both of the diseases (restrictive cardiomyopathy: RV: 13, 6, 14 mm Hg, LV: 21, 12, 19 mm Hg; constrictive pericarditis: RV: 12, 13, 16 mm Hg, LV: 16, 13, 18 mm Hg), and LV end-diastolic pressure was higher than that of the right ventricle in restrictive cardiomyopathy. Whereas high-gain LV pressure sho square root sign in all cases of constrictive pericar (Fig. 1), this sign was not seen in any of the restric cardiomyopathies (Fig. 2). In the pressure tracing corded simultaneously with a fluid-filled system a tip manometer system, square root sign was seen in the tracing with a fluid-filled system in restric cardiomyopathy (Fig. 3). Hemodynamic parameter these 6 patients are summarized in Table I with normal values of our laboratory.[4,5] Whereas the derivative curve of LV pressure in constrictive p carditis showed some characteristics of that of nor left ventricle, that is, the negative deflection of the derivative curve was much larger than the positive flection,[4] the negative deflection was much smaller t the positive in restrictive cardiomyopathy. The ind of LV relaxation were in the normal range in constric

pericarditis, and relaxation was markedly prolonged in restrictive cardiomyopathy.

Restrictive cardiomyopathy is frequently associated with systemic infiltrative diseases, and the idiopathic form is very rare. The possibility of secondary cardiomyopathy was ruled out in all 3 cases with the histologic examination of the biopsy specimens, which showed thickening of the endocardium and moderate myocardial fibrosis without any infiltrative substance.

The similarity of this disease to constrictive pericarditis has been emphasized because of elevated ventricular filling pressures, normal systolic function, and square root sign of the diastolic pressure curve. Although Meaney,[1] Benotti,[3] and their co-workers included this sign in their diagnostic criteria of restrictive cardiomyopathy, Chew et al[6] did not find this sign in their 3 patients with cardiac amyloidosis whose LV pressures were recorded with a tip manometer system. For the production of square root sign, an accelerated filling rate during early diastole and a later plateau are necessary. LV filling rate was reported to be accelerated with a later plateau,[1,2] or uniformly depressed during whole diastole[2,6,7] in cardiac amyloidosis. This difference has been postulated as being the result of uneven distribution of amyloid in the myocardium in some cases.[2,7] Although Tyberg et al[7] found square root sign in their patients with cardiac amyloidosis with a uniformly depressed diastolic filling, they suspected this was due to the artifact of fluid-filled system. This phenomenon, "pseudo-square root sign," was demonstrated by the simultaneous recordings of the pressure with a fluid-filled system and a tip manometer system (Fig. 3).

Normal relaxation, normal compliance during early diastole, and sudden elevation of stiffness of the ventricle are necessary for the production of an accelerated early diastolic filling with a later plateau, and therefore the production of square root sign. In constrictive pericarditis, LV relaxation was normal, and LV compliance must be normal until the ventricle is constricted with the stiff pericardium. Therefore, square root sign is expected in this disease from these pathophysiologic points. On the other hand, restrictive cardiomyopathy is characterized by stiff ventricle by definition, and LV relaxation was markedly prolonged. We wonder how such a stiff ventricle could dilate quickly only during early diastole. Although our experience is limited to only 3 patients, abnormal relaxation, stiff ventricle, and hence absence of square root sign seem to be prerequisite factors for restrictive cardiomyopathy.

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Myocardial Infarction Complicated by Rupture of Both Ventricular Septum and Right Ventricular Papillary Muscle

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Rupture of a right ventricular (RV) papillary muscle is an extremely rare event during acute myocardial infarction (MI).[1] This report describes a patient with this complication.

A 74-year-old man with no history of heart disease was admitted after several days of intermittent chest discomfort and after an electrocardiogram showed new Q waves in leads III and aVF. Initial examination revealed a normal blood pressure, clear lungs, no jugular venous distention, and a previously noted grade 2/6 systolic ejection murmur along the left sternal border. Two days later, the patient had prolonged chest pain, accompanied by S-T segment elevations in leads II, III and aVF. Examination now disclosed pulmonary rales, jugular venous distension to the angles of the jaw with the patient sitting upright, and a new grade 3/6 coarse holosystolic murmur heard at the apex and the lower left sternal border. Catheterization (Swan-Ganz) revealed a left-to-right intracardiac shunt at the RV level (Table I).

The patient's condition gradually deteriorated over the next 10 days. At cardiac catheterization, the right coronary artery was totally obstructed (midportion) without significant stenosis in any major left coronary artery. Left ventricular cineangiography demonstrated a ventricular septal defect with a large shunt into a dilated right ventricle. The markedly elevated right atrial pressures with large v waves suggested tricuspid regurgitation (TR) (Table I). At surgery, the ventricular septal defect was repaired with a Dacron® patch. The posterior papillary muscle of the tricuspid valve was seen to have a necrotic tip which had ruptured completely; the valve was replaced with a procine bioprosthesis. The patient was discharged 1 month later and has been followed up for 18 months with no chest pain or limitation of activity.

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TABLE I Catheterization Data

Site	Day 4 Pressure (mm Hg)	Day 4 O_2 Sat (%)	Day 14 Pressure (mm Hg)	Day 14 O_2 Sat (%)
Inferior vena cava	. . .	. . .	. . .	59
Superior vena cava	. . .	. . .	. . .	38
Mean right atrial pressure	5	66	16	57
a wave	. . .	. . .	22	. . .
v wave	. . .	. . .	26	. . .
Right ventricle	48/5	82	53/20	78
Pulmonary artery	44/12	90	57/18	75
Mean pulmonary capillary wedge pressure	10	. . .	20	. . .
Ascending aorta	. . .	98	88/52	87
Left ventricle	. . .	. . .	88/22	. . .

O_2 Sat = oxygen saturation.

TR is an uncommon complication of MI.[1–6] The most likely cause of TR in this setting would be MI involving a tricuspid valve papillary muscle, with associated akinesia or dyskinesia of adjacent RV wall. This mechanism is analogous to that postulated to produce mitral regurgitation during MI. One would therefore expect TR in these circumstances to be associated with a posterior wall left ventricular MI with accompanying RV infarction.

A review of previous reports disclosed 7 cases of TR complicating MI. All occurred after an inferior wall MI. Tricuspid valve papillary muscle infarction with rupture was found at autopsy in 1 case,[1] and infarction without rupture was noted at autopsy in another.[2] Tric valve papillary muscle infarction without ruptur seen at the time of surgical replacement of the tric valve in 1 patient.[3] In a fourth case, the tricuspid was replaced, but the morphologic findings wer reported.[4] TR was diagnosed in 3 other patients years after an inferior wall MI; the diagnosis was clinically in 1 patient[5] and confirmed with right-cardiac catheterization in 2 others.[5,6]

The patient described in this report had a lar involving the walls of both ventricles, complicat a ruptured tricuspid valve papillary muscle and tured ventricular septum. The TR was exacerbat the RV MI, and was made even worse by the seco pulmonary hypertension and the large left-to shunt across the ventricular septal defect. Th volume overload and elevated pressure probably tributed to the rupture of the infarcted tricuspi pillary muscle; the low-pressure RV characteristic account for the extreme rarity of such an event.

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Demonstration of Prostaglandin E_2 and $F_{2\alpha}$ in Atrial Tissue of Patients With Heart Disease

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Prostaglandin (PG) synthesis has been demonstrated in a variety of cardiac tissue preparations from experimental animals.[1–4] Although PG has been reported in blood samples of the coronary sinus in human beings,[5] no data on PG concentration in human cardiac tissue have been reported. This investigation sought to identify PG and to estimate the amount present in the atria of patients with heart disease.

PGE_2 and $PGF_{2\alpha}$ were determined in atrial tissue of 6 patients (2 men and 4 women) at the time of cardiac surgery.

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The diagnosis was mitral stenosis in 4 patients, atrial s defect in 1, and aortic regurgitation in 1. All patients in New York Heart Association functional class II o Their ages ranged from 23 to 52 years. The samples obtained at surgery, briefly washed in cold Krebs solu and weighed. The tissues were stored at −20°C for s quent homogenization with a mortar and pestle in aqueous ethanol and sand; the homogenate was stirre 2 hours at room temperature (4 ml/g of tissue). The mi was centrifuged at 1,000 rpm and the supernatant acidified to pH 3 with formic acid (98%). After extra of acidic lipids from the supernatant and separation by acid chromatography (100 mesh, Mallinckrodt), we d mined PGE_2 and $PGF_{2\alpha}$ concentration by radioimmuno using Dray's method.[6]

TABLE I Prostaglandin (PG) Concentration in Atrial Tissue of Patients With Heart Disease (ng/mg Protein)

Diagnosis		Right Atrium PGE_2	Right Atrium $PGF_{2\alpha}$	Left Atrium PGE_2	Left Atrium PGF
MS	M	52	25	107	91
MS	F	50	26	110	95
MS	F	52	27	116	92
MS	F	. . .	. . .	163	90
ASD	F	20	11	. . .	. . .
AR	M	19	14	24	13

AR = aortic regurgitation; ASD = atrial septal defect; MS = n stenosis.

Unlabelled PG was obtained from Upjohn, tritiated tracer from New England Nuclear, and the appropriate antiserum from the Pasteur Institute. The overall recovery after purification (extraction and chromatography) was between 75 and 85%. Protein was measured by the method of Lowry et al.[7]

We demonstrated that PG is present in human atrial tissue. It is possible that PG might participate in the cardiac response to certain forms of heart disease (Table I). No inference can be made about the concentration of PG in the normal human heart under physiologic conditions.

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Selective Coronary Angiography by Translumbar Aortic Puncture

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Multivessel coronary artery disease is frequently present in patients when aortoiliac and cerebrovascular occlusive disease coexist. In this group of patients surgical relief of carotid and iliofemoral arterial stenosis without myocardial revascularization carries a significant risk of perioperative myocardial infarction.[1] In some patients, arterial access for angiography is impossible because all peripheral pulses are absent. Whereas intravenous digital subtraction angiography[2] can provide adequate visualization of the aortic arch and extracranial cerebral vasculature, there is no substitute for selective coronary angiography. A patient is described in whom selective bilateral coronary angiography was performed by way of the translumbar aortic approach.

A 49-year-old man with aortoiliac and bilateral carotid arterial stenosis underwent unsuccessful attempts at arterial catheterization from both femoral and left axillary arteries. An intravenous digital subtraction angiogram demonstrated occlusion of the innominate and left subclavian arteries and subtotal obstruction of the left common carotid artery. In view of the widespread atherosclerosis, significant multivessel coronary arterial disease was suspected and selective coronary angiography through the translumbar route was performed. We believed that selective coronary catheterization was best performed by preshaped catheters, which are most safely introduced through an introducer sheath. A 30-cm-long introducer sheath was prepared from 0.131-inch (outer diameter) clear Teflon® angiographic tubing (Angiograf, Inc.), which accepted a 7F Judkins catheter. The tip was tapered to 0.118 inch. The proximal end of the sheath was fitted with a hemostat valve over a Luer-Lock adapter. Another 45-cm-long 7F Teflon angiographic tubing was tapered over a 0.038-inch spring guide to act as a dilator (Fig. 1). With the patient in the prone position a standard "upstream" translumbar puncture was made below the twelfth rib 6 to 8 cm lateral to the midline with an 18.0 gauge translumbar needle with a Teflon sheath in a steep oblique fashion. Once the aortic lumen was entered, a 0.038 inch J-tip guide wire was introduced and the sheath was deflected into the thoracic aorta. The 18.0 gauge sheath was removed and the soft tissue tract was dilated with use of nephrostomy dilators, taking care not to puncture the aorta. Then the 45-cm-long 7F dilator was fitted in a coaxial fashion into the introducer sheath and the whole system was introduced into the aorta, without any difficulty over the guide wire. The guide wire and the dilator were removed and selective catheterization of both coronary arteries was performed using the Judkins technique without difficulty (Fig. 2). After the procedure, computed tomographic images of the retroperitoneum were obtained. A small amount of periaortic hemorrhage was seen as slight thickening of the left crux of the diaphragm (Fig. 3). The patient's hematocrit was unchanged during the next 2 days. The patient subsequently had saphenous venous grafts to the left anterior descending and right coronary arteries.

Catheter translumbar aortography, introduced by Amplatz[3] in 1963, significantly decreased the complications of the needle translumbar technique. Stocks et al[4] described a modification of Amplatz's technique in

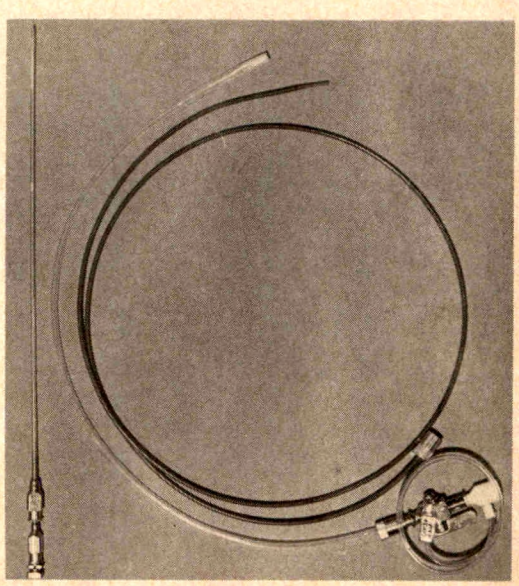

FIGURE 1. The standard 18.0-gauge translumbar needle assembly and coaxial introducer sheath.

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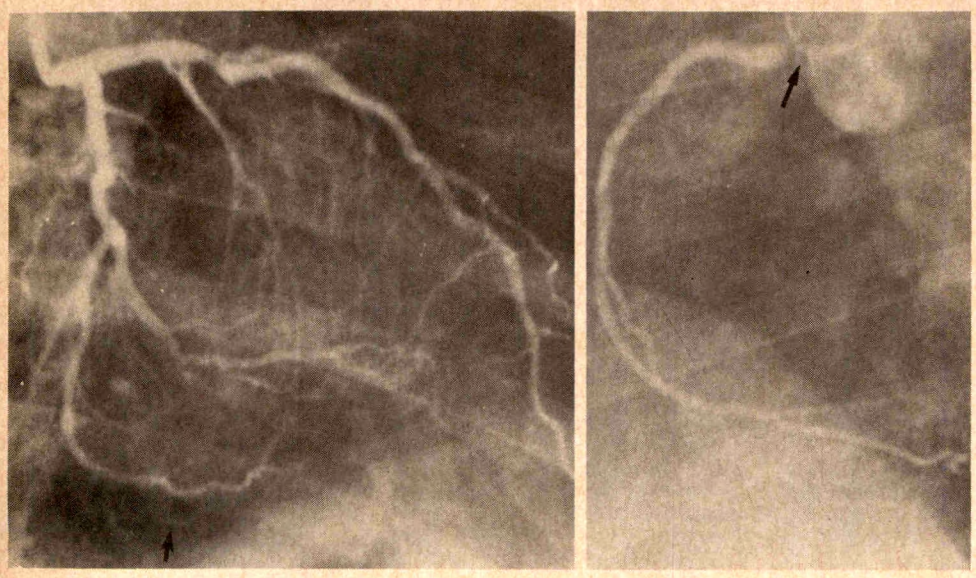

FIGURE 2. Left, selective left coronary angiogram in the right anterior oblique projection. There is moderate stenosis of the midportion of the left anterior descending artery. Note the collateral flow to the right coronary artery (**arrow**). **Right,** left anterior oblique projection of the right coronary angiogram reveals severe stenosis at the origin of the right coronary artery (**arrow**).

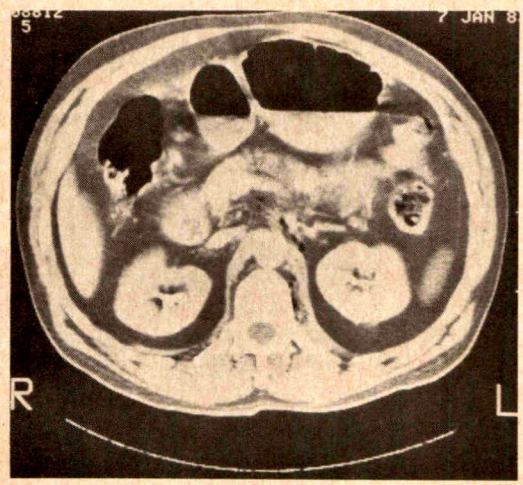

FIGURE 3. Computed tomographic scan of the abdomen 1 cm below the level of the aortic puncture site. Note the thickening of the left crux of the diaphragm caused by small amounts of periaortic hemorrhage.

1969, wherein they substituted a 60-cm-long needle and Teflon sleeve so that aortic arch and selective cerebral angiography could be performed. Recently, Maxwell et al[5] described a patient similar to ours in whom they performed selective catheterization of a dominant left coronary artery by substituting a preshaped catheter for the Teflon sleeve described by Stocks et al.[4] We, too, believed that exchange of a preshaped catheter would not be feasible using their technique. It would not have been possible to obtain enough torque control to perform catheterization using Sones' technique. Hence, we used an introducer sheath. We were apprehensive about the diameter of the sheath and were pleasantly surprised to note the inconsequential amount of periaortic hemorrhage in the computed tomographic scan performed after the procedure. However, with this technique there is a greater risk of significant retroperitoneal hemorrhage than with standard translumbar aortography. Hence, we believe that this technique is a safe and worthwhile alternative to coronary angiography in patients in whom there is no other access to the vascular system.

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Idiopathic Severe Bilateral Atrial Dilation

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Idiopathic dilation of the right atrium is a rare anomaly, with 30 cases having been described. The etiology is considered congenital. The patients had dyspnea, fatigue, atrial fibrillation, and pulmonary emboli. Pericardial taps were performed because of false diagnosis of pericardial effusion. Differential diagnosis from valvular heart disease is difficult.[1–3] Idiopathic dilation of both atria is extremely rare.[4] In addition to all these complications, dilation of both atria may also be asso-

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ciated with systemic embolization. We report the first case of this anomaly diagnosed antemortem.

A 24-year-old pregnant woman was referred to us because of progressive dyspnea. At age 20 years, atrial fibrillation had developed. Delivery occurred at 8 months of pregnancy. Two weeks later transient left hemiparesis developed. No signs of congestive heart failure or cyanosis were found. The heart rate was irregular (80 beats/min). Blood pressure was 110/60 mm Hg. Both heart sounds were accentuated and the second sound was not split. A systolic murmur (grade 1/6) was heard over the upper left sternal border. A short mid-diastolic murmur was heard over the apex. The electrocardiogram showed atrial fibrillation and left-axis deviation. The thoracic roentgenogram showed cardiac enlargement, mainly due to enlargement of both atria. The pulmonary artery segment was prominent. Echocardiography demonstrated marked dilation of both atria. All cardiac valves were normal; however, a fine diastolic flutter of the anterior mitral leaflet was demonstrated. Radionuclide cardiac imaging demonstrated marked dilation of both atria, a left ventricular ejection fraction of 63%, and a right ventricular ejection fraction of 54%. Cardiac catheterization and angiocardiography confirmed biatrial dilation and revealed no shunt or obstructive lesion. Ventricular anatomy and contractility were normal, and so were the pressures in the cardiac chambers and great arteries. No signs of thrombus were seen. Routine laboratory tests including thyroid function tests revealed no abnormal findings.

The etiology of idiopathic biatrial dilation is unclear. Studies of idiopathic dilation of the right atrium revealed a partial loss of atrial muscular fibers, irregular thickening of muscle fibers, lipomatous degeneration and lymphocytic infiltration of the atrial wall, and no signs of rheumatic heart disease. Congenital etiology or changes after myocarditis were suggested by most investigators[1,2,5,6] to explain the pathogenesis.

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Acute Myocardial Infarction 14 Years After an Acute Episode of Kawasaki's Disease

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Kawasaki's disease is an acute febrile illness of young children.[1] Coronary artery aneurysms have been described in 15% of patients during the acute disease.[2] Death attributed to occlusion or rupture of coronary artery aneurysms occurs in 1 to 2% of patients.[3] Symptomatic coronary artery involvement usually occurs within months of the acute disease and rarely presents for the first time in adults.[2–4] Such was not the case in the patient described herein.

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A 23-year old male smoker was hospitalized with retrosternal chest pain lasting 3 hours. Findings on physical examination were normal, but the electrocardiogram showed S-T segment depression in leads V_1 to V_4. Creatine phosphokinase (CPK) level on admission was 1,008 U/liter. The pain subsided rapidly, and the patient was asymptomatic for the next 10 days. Serial electrocardiograms demonstrated the development of small Q waves in leads II, III, and aVF, and the CPK level returned to normal. A graded effort test performed 10 days after admission was stopped after 5 minutes because of chest pain and S-T segment depression of 1.5 mm. Coronary angiography performed 14 days after

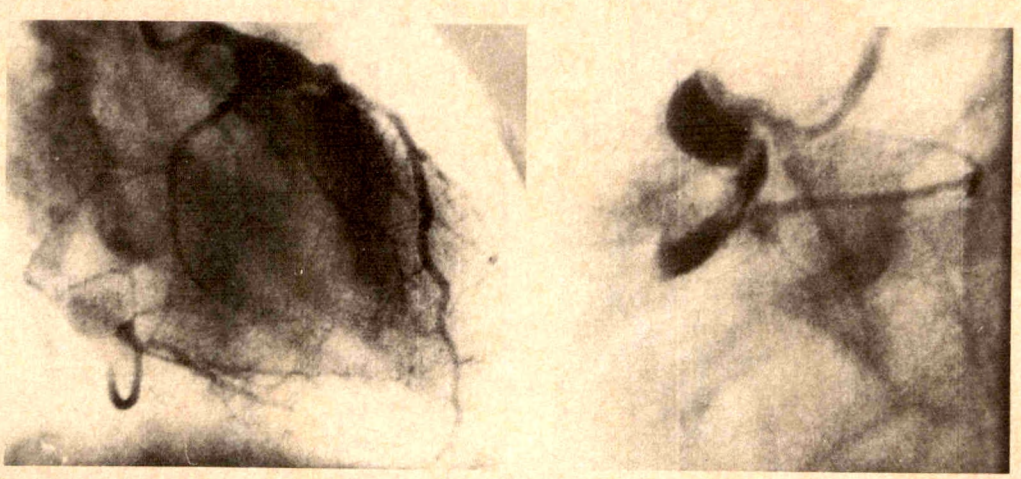

Figure 1. Left, left coronary artery injection (right anterior oblique view) showing a large aneurysm of the left main coronary artery extending to the left anterior descending and circumflex arteries. The distal right coronary artery is demonstrated (**bottom left** of photograph). The distal coronary arteries are normal. **Right,** right coronary artery injection (left anterior oblique view) showing a large aneurysm at the origin of the artery. Contrast material surrounds a big thrombus. No anterograde filling of the artery is demonstrated.

admission showed a large aneurysm of the left main coronary artery extending to the left anterior descending and left circumflex arteries. The distal right coronary artery filled from the left system (Fig. 1, left). A large aneurysm at the origin of the right coronary artery contained thrombus without anterograde filling of the vessel (Fig. 1, right). Ventriculography demonstrated good left ventricular function with a small area of hypokinesia in the inferior wall. The patient was discharged on warfarin and beta blockers and was scheduled for coronary bypass surgery.

At age 9 years, he had been hospitalized for a febrile episode associated with buccal ulceration, bilateral conjunctivitis, and disseminated rash. This had not improved with antibiotic treatment. After 5 weeks, the symptoms and signs had disappeared and the patient remained in good health without physical limitation until the present admission. Although the diagnosis of Kawasaki's disease had not been made at that time, the characteristic acute episode as well as the current typical angiographic findings were considered evidence that the patient had this disease.

Before angiography, the tentative etiologic diagnoses in this young adult were either coronary atherosclerosis associated with smoking[5] or possible coronary artery spasm due to heavy alcohol intake with normal coronary arteries.[6] The typical angiographic findings and the febrile illness at age 9 years provided sufficient evidence to diagnose Kawasaki's disease. The long interval between the acute disease and the first presentation of coronary artery involvement obscured the relation between the illness at age 9 years and the acute myocardial infarction at age 23. Our case illustrates the importance of coronary angiography in young adults with ischemic heart disease. In all young patients with ischemic heart disease, a careful search for a history compatible with Kawasaki's disease should be carried out.

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LETTERS*

RELATION OF HIGH-INTENSITY EXERCISE TO RECURRENCE RATE OF MYOCARDIAL INFARCTION AND/OR CORONARY DEATH

We read the article by Rechnitzer et al[1] showing that high intensity endurance exercise does not reduce myocardial infarction (MI) rate or coronary death beyond activity that fails to produce a training effect. The results were not unexpected. Endurance exercise failed to reduce reinfarction and coronary death rates in another well-conceived postinfarction exercise trial.[2] The authors cite the multifactorial approach by Kallio et al,[3] which demonstrated a lower incidence of sudden death in postinfarction patients and included exercise in their intervention. However, exercise was probably not a factor in reducing sudden death, as the intervention group failed to demonstrate a training effect.

Epidemiologic investigators concerned with the mode of exercise and coronary disease have found that exercise other than the endurance type (i.e., share croppers[3] and longshoremen[4]) has resulted in reduced untoward cardiovascular events. The study by Paffenbarger and Hale[5] points out that only cargo handlers engaged in burst activities of pushing, pulling, and lifting cargo had a reduced incidence of sudden cardiac death. Other longshoremen not engaged in this form of activity did not show coronary benefit. In summary, endurance exercise has failed to produce beneficial results in prospective trials, and cardiovascular risk benefits are not well supported by epidemiologic research. It may be more important to train individuals in another manner. Burst activity utilizing resistance to the exercise (such as pushing, pulling, and lifting) may help provide answers to the question of exercise benefits in the prevention of coronary heart disease.

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4. **Cassel J, Heyden S, Bartel AG, Kaplan BH, Tyroler HA, Cornoni JC, Hames LG.** Occupation and physical activity and coronary heart disease. Arch Intern Med 1971; 128:920–928.
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*Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

LEFT ISOMERISM (POLYSPLENIA SYNDROME) AND COMPLETE ATRIOVENTRICULAR BLOCK

Garcia et al[1] reported an apparent association between left isomerism and complete atrioventricular block. They presented a total of 9 cases of left isomerism and congenital complete AV block (4 cases of their own and 5 from the literature), and 2 cases of acquired nonsurgical complete AV block associated with left isomerism. To this experience we add 2 cases of congenital complete AV block and left isomerism, and additional published evidence to support the association between complete AV block and left isomerism.

A 2.5-kg, 36-week gestation infant was transferred to our hospital at 1 hour of age for management of hydrops fetalis and complete AV block, which had been diagnosed in utero elsewhere. Cardiac catheterization at 12 hours of age showed double-outlet right ventricle, D-transposition of the great arteries, common atrium, partial anomalous pulmonary venous return to the right side of the common atrium, patent ductus arteriosus, interrupted inferior vena cava with continuation to the azygos system, and abdominal heterotaxia. The electrocardiogram showed complete AV block and superior axis of the P wave. A temporary transvenous ventricular pacing catheter was placed after cardiac catheterization. Digoxin and diuretic therapy was begun. One week later, at a postdiuresis weight of 2.2 kg, a permanent epicardial demand ventricular pacemaker was implanted and the patent ductus arteriosus was ligated. A technetium liver-splenic scan confirmed the presence of splenic tissue. The patient did well postoperatively, and remains well at 15 months of age.

The second patient was born by Cesarean section for fetal bradycardia at 38 weeks' gestation. At birth hydrops fetalis, respiratory distress, and a ventricular rate of 65 beats/min were noted. The electrocardiogram showed complete AV block and superior axis of the P wave, a diagnostic sign of polysplenia syndrome.[2] The chest x-ray showed mesocardia, cardiomegaly, bilateral hyparterial bronchi, increased pulmonary vascularity, and abdominal heterotaxia. She died at 24 hours of age with intractable heart failure.

In addition to our personal experience, 3 additional cases are reported in the literature. Shenker[3] reported a case of intrauterine complete heart block and polysplenia syndrome. The infant died at 2 weeks of age, and necropsy showed atrial septal defect, ventricular septal defect, anomalous pulmonary venous return, and multiple spleens. Sokol et al[4] reported a case of intrauterine complete heart block and polysplenia syndrome. This infant (33 weeks' gestation) died 28 hours after birth, and necropsy showed endocardial cushion defect and interrupted inferior vena cava with continuation to the azygos system. Morphologic examination of the conduction system disclosed fibrosis in the atrium and AV node. Kleinman et al[5] reported a case of congenital complete AV block (diagnosed by fetal echocardiography) and polysplenia syndrome. This infant was born at 34 weeks' gestation and had hydrops fetalis, levocardia, and endocardial cushion defect. This infant died 10 minutes after birth.

As did Garcia et al,[1] we emphasize that left isomerism with complex cardiac defects is often associated with complete AV block. Also, this association should be recognized as the most common cause of death in infants with congenital complete AV block. Since cardiac anomalies in left isomerism are often amenable to surgery, aggressive management is warranted. The potential results are demonstrated by our first patient who, to our knowledge, is the smallest infant to accept a permanent epicardial pacemaker. This infant is the only one reported with left isomerism and congenital complete heart block surviving past 1 year of age. In the Garcia et al[1] series, all 4 newborns with congenital heart block died by age 2 months. With the existence of perinatal centers and availability of fetal echocardiography, this complex cardiac disease should be diagnosed in utero.

Ashok V. Mehta, MD
Guillermo R. Sanchez, MD
Philadelphia, Pennsylvania

1. **Garcia OL, Mehta AV, Pickoff AS, Tamer DF, Ferrer PL, Wolff GS, Gelband H.** Left isomerism and complete atrioventricular block: a report of six cases. Am J Cardiol 1981 (Dec);48:1103–1107.
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BYPASS GRAFTING IN TOTAL OCCLUSION OF THE LEFT MAIN CORONARY ARTERY

I have read the article by Esente et al[1] about coronary collateral protection. My purpose in responding is to point out that present-day treatment would have been more aggressive in revascularizing their patient. Although at 32 months the patient is reported to be asymptomatic, it has been demonstrated that long-term survival and symptomatic relief are limited by diseased ungrafted coronary arteries.

The 2 arteriographic frames presented illustrate a 100% left main occlusion, a 70 to 80% mid-left anterior descending (LAD) stenosis, and a 50% right coronary artery stenosis. The proximal anatomy is cut off on the frame, but it appears that a dominant diagonal would definitely not be satisfactorily revascularized from the LAD nor from the left circumflex graft. A 50% stenosis in the right coronary artery warrants grafting at the

time of left-sided revascularization. With present-day myocardial protection, complete revascularization has been greatly simplified and complete revascularization is usually necessary.

Thomas A. Orszulak, MD
Rochester, Minnesota

1. **Esente P, Arquin PL, Giambartolomei A, Gensini GG.** Extreme protective action of coronary collateral vessels in completely occlusion of the left main coronary artery. Am J Cardiol 1982;50: 1441–1445.

UNSTABLE ANGINA PECTORIS: CORRECTION OF ERROR IN PREVIOUS REPORT

In our report on the management of unstable angina,[1] we stated that 77 of our 100 cases followed up for 1 year remained free of "significant symptoms." This should have read "significant complications." In fact, 36 of the 96 28-day survivors complained of angina pectoris during some or all of the follow-up period.

This error in the text of our report has given rise to misunderstanding and to questions about the comparability of our diagnostic criteria with those of other studies.[2] We would like to confirm that our diagnostic criteria conform closely to those of the Framingham Study[3] and the National Cooperative Study Group.[4]

This correction had already been conveyed to the previous Editor of the *Journal* but failed to be published because of the change in journal management.

Risteard Mulcahy, MD, FRCP, FRCPI
Dublin, Ireland

1. **Mulcahy R, Daly L, Graham I, Hickey N, O'Donoghue S, Owens A, Ruane P, Tobin G.** Unstable angina: natural history and determinants of prognosis. Am J Cardiol 1981;48:525–528.
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3. **Kannel WB.** The Framingham Study: an epidemiological investigation of cardiovascular disease. National Center for Health Statistics, 1974. Section 30:20 (DHEW Publications 74–599).
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TRANSMURAL VERSUS NONTRANSMURAL MYOCARDIAL INFARCTION

We are surprised that, for one so obsessed with semantic clarity, Dr. Spodick chose to use a quotation from our article so loosely and out of context in order to strengthen his own argument for discarding the terms "transmural" and "nontransmural (subendocardial)" for classifying acute myocardial infarction.[1] In making the statement "regardless of the terms used . . . ," we were not suggesting that terminology should be disregarded or is unimportant. Rather, we were making the point that *whatever* terminology is used, it was our experience that patients with infarcts manifested by Q waves differed from those without Q waves. The full text of that segment of our paper reads: "Spodick has suggested that infarcts should be designated according to the presence or absence of Q waves and not by the traditionally used terms of subendocardial or nontransmural. Regardless of the terms used, our studies and those of other investigators suggest that, at least clinically, the absence of Q waves in patients with acute myocardial infarction appears to identify a group whose immediate and subsequent clinical courses differ from those of patients with Q waves."[2] I should point out in all fairness that not everybody agrees with even this statement![3]

If a distinction is to be made, I submit that "Q wave infarct" and "non–Q wave infarct" are more comprehensive than Spodick's classification of Q wave infarction and S-T infarction. Although it is rare, it is possible to have myocardial infarction with neither Q waves nor S-T segment abnormalities showing on the standard electrocardiogram.

Roman W. DeSanctis, MD
Adolph M. Hutter, Jr., MD
Boston, Massachusetts

1. **Spodick DH.** Q wave infarction versus S-T infarction: nonspecificity of electrocardiographic criteria for differentiating transmural and nontransmural lesions. Am J Cardiol 1983;51:913–915.
2. **Hutten AM Jr, DeSanctis RW, Flynn T, Yeatman LA.** Nontransmural myocardial infarction: a comparison of hospital and late clinical course of patients with that of matched patients with transmural anterior and transmural inferior myocardial infarction. Am J Cardiol 1981;48: 595–602.
3. **Phibbs BD.** "Transmural" versus "Subendocardial" myocardial infarction: an electrocardiographic myth. J Am Coll Cardiol 1983;1:561–564.

REPLY: DeSanctis and Hutter posit 3 considerations: (1) appropriate quotation, (2) results of their studies, and (3) improved terminology. They have contributed their complete quotation so that the readers can decide for themselves whether the material quoted was—for the purpose intended—out of context. It certainly was not loosely chosen. My own complete quotation was: "Indeed, investigators of the highest intellect and skill—despite *explicitly acknowledging the material cited in References 1–3*,—write 'regardless of the terms used . . . ,' implying that slipshod terminology is unimportant." This formulation was designed to simultaneously acknowledge their work (emphasis added) and isolate the point of my essay—disregard for accurate labels—with the elision indicating incomplete quotation. References 1 to 3 referred to my letters in 3 journals in 1980, 1981, and 1982, extensively documenting the lack of correlation between electrocardiography and anatomy. Because letters were ineffective, it was (as the editor can confirm) their report that finally led to a more formal attempt to set things right. DeSanctis and Hutter have missed the point of my essay; terminology was in question, never their scientific material, and I hope my quotation of Confucius (p. 914) set the tone.

I hope these efforts make clear that my concern is with *conceptual* clarity—which appropriate terminology can either enhance or debase (Cf. Confucius). The important thing is to call things as we see them. What we *actually see* on the ECG is how we should label an infarct, keeping in mind that the ECG cannot tell us the anatomic extent of the infarct, but is telling us something else that should require further investigation. The data in their paper is a meticulous contribution to the distinction between Q wave and non–Q wave infarcts. Indeed, it should further stimulate those who wish to learn why the ECG separates infarcts into certain clinical and prognostic groups, but cannot reliably distinguish their anatomy. Finally, DeSanctis and Hutter have improved my classification by mentioning that the rare possibility of infarction with neither Q waves nor S-T segment abnormalities could not be called S-T infarction (although the vast number of non-Q wave infarcts can be). I believe I can make their proposal even more comprehensive. Like our colleagues who distinguish A, B, and "non-A non-B" hepatitis, perhaps we could designate Q, S-T, and "non-Q non-S-T" infarctions.

David H. Spodick, MD, DSc
Worcester, Massachusetts

MYOCARDIAL METABOLIC ALTERATIONS AFTER CONTRAST ANGIOGRAPHY

The article by Wisneski et al[1] demonstrated that contrast medium alters the myocardial uptake of various substrates. Their results suggested that the changes in myocardial uptake of lactate and glucose could be related to a decrease of the arterial level of free fatty acids induced by the contrast medium. The authors mentioned, however, that all patients received heparin (10,000 U) as an intravenous bolus before the arterial puncture. Heparin has a lipolytic effect and induces a release of free fatty acids with an initial increase of this substrate, followed by a decrease. Thus, how much time elapsed between the administration of heparin and the first sampling point?

The authors mentioned that blood samples were obtained at 3 and 10 minutes to ensure a steady metabolic state, but one can suspect that these 2 samples could concern 2 points symmetrically located on the ascending and descending branch of the peak after the injection of heparin.

Another point concerns the expression of the results. These were presented in terms of myocardial uptake, i.e., the product of coronary sinus blood flow by arteriovenous difference of the substrate. Their Figure 8 suggests a transient increase of coronary sinus blood flow. What happened to the arteriovenous difference? Does the contrast medium convert a normal myocardial extraction (A > V) of lactate in a production (V > A) of lactate, usually considered a metabolic marker of ischemia?

Michel E. Bertrand, MD
Lille, France

1. **Wisneski JA, Gertz EW, Neese R, Soo WJ, Bristow JD, Adams JR, Beaudry JP:** Myocardial metabolic alterations after contrast angiography. Am J Cardiol 1982; 50:239–245.

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Prescribing Information Tablets of 50 mg
Tablets of 100 mg

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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experts agree the preference for one beta-receptor over the other is not absolute.

CME Test #2

Coronary Reperfusion and Bezold-Jarisch Reflex*

The University of Alabama School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marked on the instruction sheet on page A135.

1. The Bezold-Jarisch reflex is characterized by:
   a) tachycardia and hypertension
   b) bradycardia and hypertension
   c) tachycardia and hypotension
   d) bradycardia and hypotension

2. It is known that the receptors that induce the Bezold-Jarisch reflex respond to:
   a) chemical stimuli
   b) mechanical stimuli
   c) metabolic stimuli
   d) all the above

3. The exact location of the receptors in man has:
   a) been primarily in the inferoposterior wall
   b) not been determined experimentally
   c) been primarily in the inferoanterior wall
   d) been in none of the above

4. In this study, arteriographic findings identified occlusions in:
   a) left anterior descending arteries of 44 cases
   b) right coronary arteries of 7 cases
   c) left circumflex coronary arteries of 13 cases
   d) all the above

5. In this study, recanalization of the occluded coronary arteries was achieved in:
   a) 34 of 40 right coronary arteries
   b) 34 of 40 left anterior descending arteries
   c) 23 of 32 left anterior descending arteries
   d) none of the above

6. In this study, it is noteworthy that in 19 of 20 cases, the Bezold-Jarisch reflex was associated with involvement of the:
   a) left anterior descending artery
   b) left circumflex coronary artery
   c) right coronary artery
   d) none of the above

7. The only occurrence of the Bezold-Jarisch reflex associated with left anterior descending recanalization was observed when this artery was the source of collateral blood flow to:
   a) an occluded right coronary artery
   b) an arterial aneurysm
   c) an occluded left circumflex coronary artery
   d) an occluded left anterior descending artery

8. On first measurements, in the representative case involving a 72-year-old man, there was:
   a) 190/26 mm Hg right ventricular pressure
   b) 190/26 mm Hg aortic pressure
   c) 188/82 mm Hg aortic pressure
   d) 188/82 mm Hg left ventricular pressure

9. This study confirmed that myocardial reperfusion is capable of:
   a) stimulating a cardiac inhibitory reflex
   b) stimulating a cardiac excitatory reflex
   c) offsetting effects of hypertensive medication
   d) causing tachycardia

10. In this study, the factor that initiates the Bezold-Jarisch reflex appears to be:
    a) neurotransmitted
    b) chemical
    c) mechanical
    d) metabolic

11. Observations in this study suggest that the occurrence of the Bezold-Jarisch reflex after coronary reperfusion is:
    a) a reliable predictor of myocardial salvage
    b) not a reliable predictor of myocardial salvage
    c) what is expected of prolonged ischemia
    d) none of the above

12. Because a vagal reflex induces hypotension and bradycardia after right coronary recanalization, it is advisable to:
    a) administer atropine prophylactically
    b) remove patient from oxygen tent quickly
    c) administer aminophylline prophylactically
    d) administer amytryptoline prophylactically

***This article appears on page 221 of this issue.**

CME Test #2: Answer Sheet

Coronary Reperfusion and Bezold-Jarisch Reflex

Instructions: Mark the appropriate box with an "X."
Test Questions appear on page A134.

1. a☐ b☐ c☐ d☐	7. a☐ b☐ c☐ d☐
2. a☐ b☐ c☐ d☐	8. a☐ b☐ c☐ d☐
3. a☐ b☐ c☐ d☐	9. a☐ b☐ c☐ d☐
4. a☐ b☐ c☐ d☐	10. a☐ b☐ c☐ d☐
5. a☐ b☐ c☐ d☐	11. a☐ b☐ c☐ d☐
6. a☐ b☐ c☐ d☐	12. a☐ b☐ c☐ d☐

Name _____ Degree _____

(please print) Last First Initial

Specialty _____ Social Security # _____

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Signature _____ Date _____

Be sure you have checked the best answer for each question. To defray costs of processing, please enclose check for $10.00 payable to the Division of Continuing Medical Education, and mail with the completed answer sheet to:

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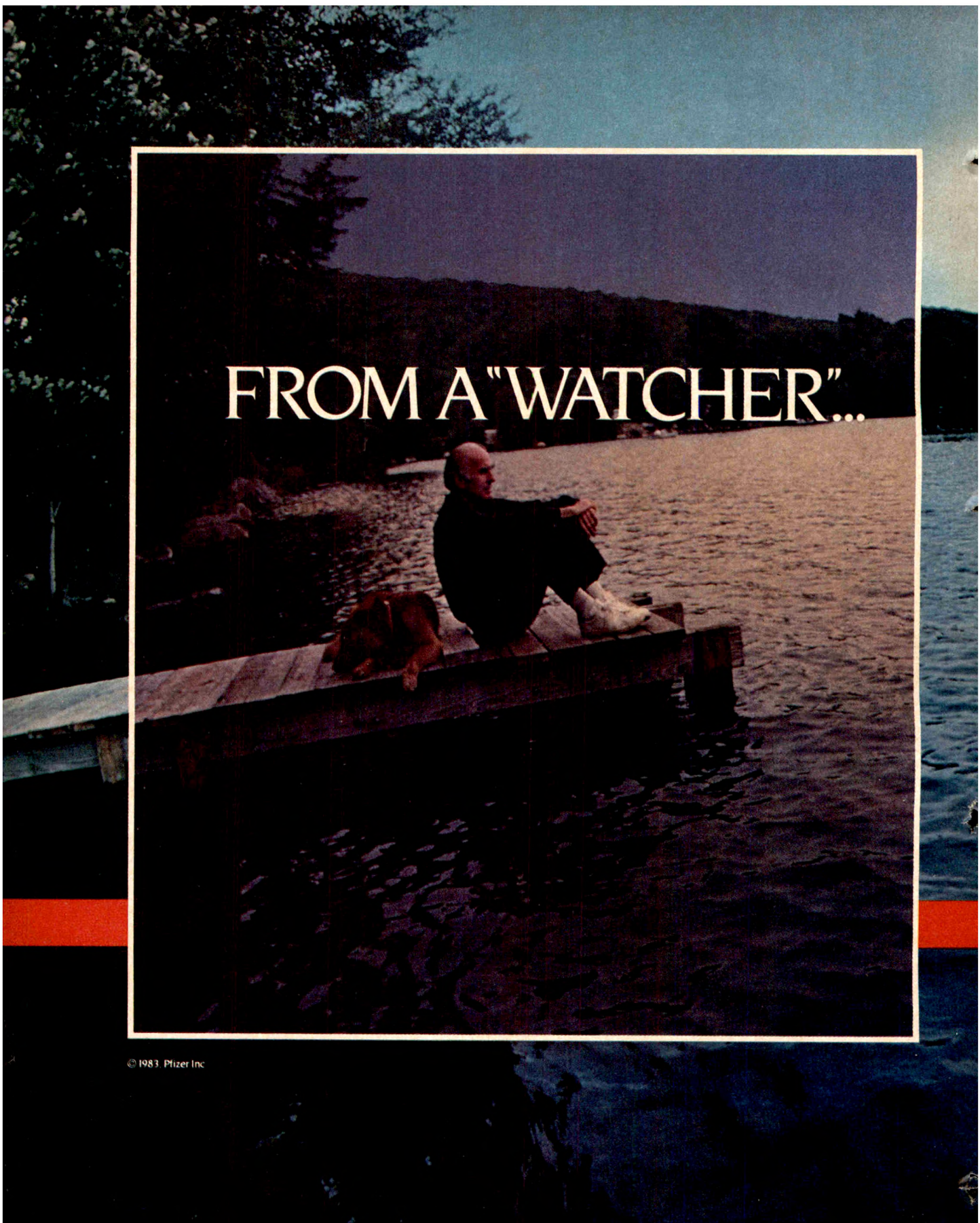

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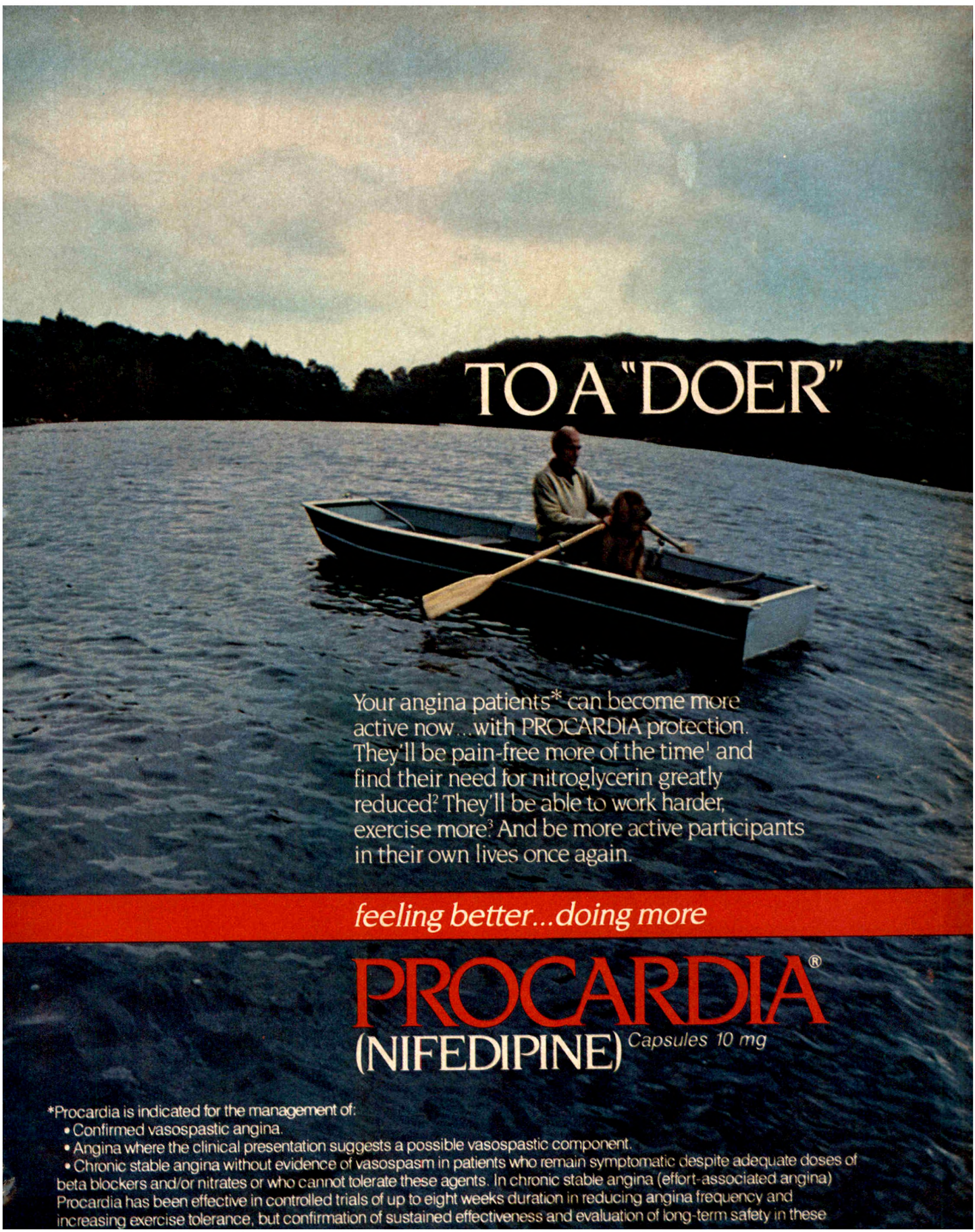

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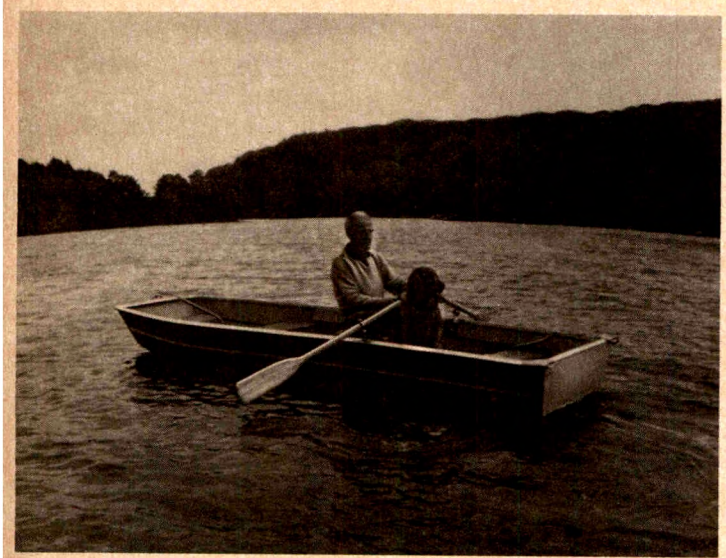

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For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

–Offers a favorable safety profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Eng J Med* 302:1269-1273, June 5, 1980.
3. De Ponti C, De Biase AM, Pirelli S, et al: Effects of nifedipine, acebutolol, and their association on exercise tolerance in patients with effort angina. *Cardiology* 68 (suppl 2): 195-199, 1981.

BRIEF SUMMARY
PROCARDIA® CAPSULES For Oral Use
(nifedipine)

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the man-

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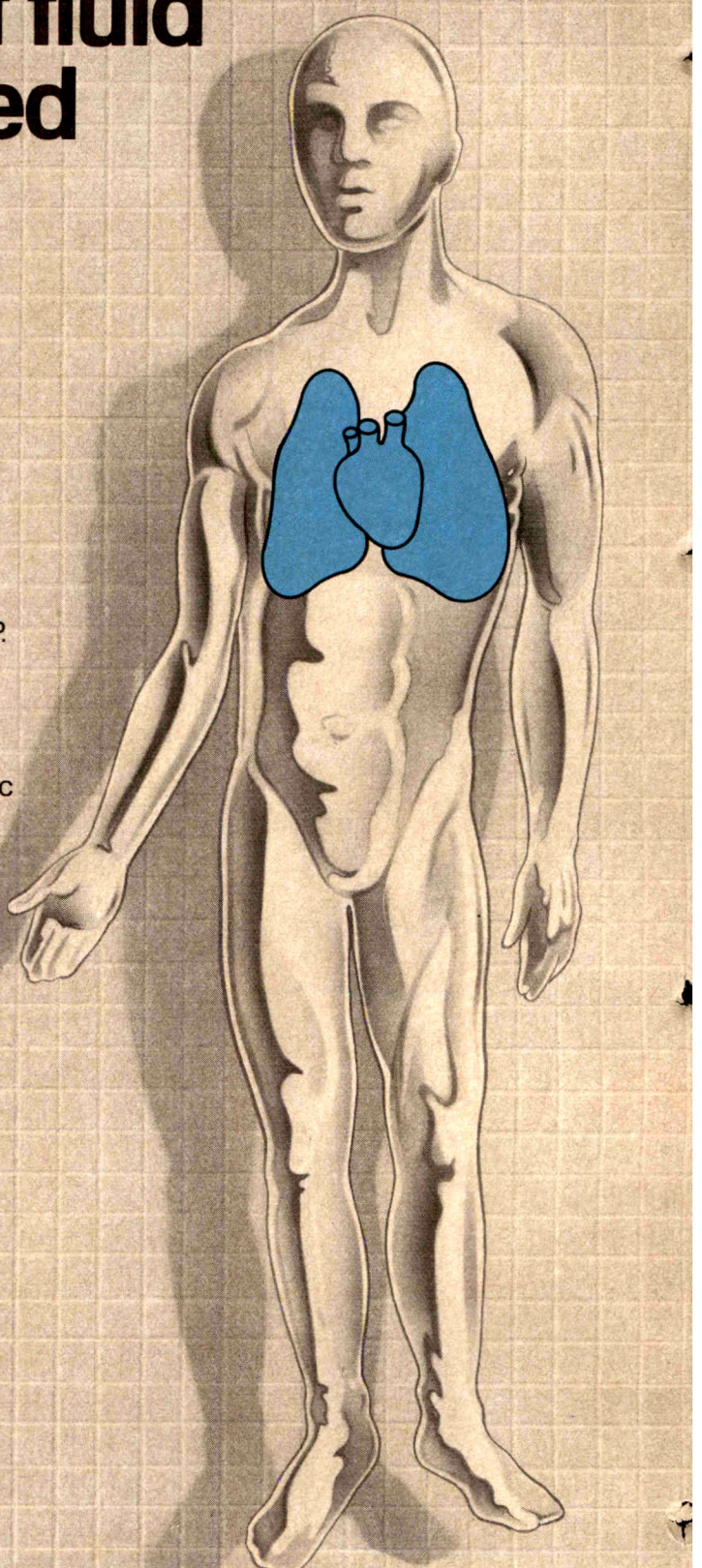
Therapeutic challenge:

Redistribution of fluid in CHF associated with acute MI



In Early CHF[1]

Pulmonary congestion with increased preload.

Findings: Elevated preload, elevated blood pressure, normal or slightly decreased cardiac output, PCWP greater than or equal to 18 mm Hg.

Therapeutic goal:
Reduce pulmonary congestion, lower PCWP to 15 to 18 mm Hg.

In Late CHF[1]

Pulmonary congestion with increased preload and afterload.

Findings: Low cardiac output, depressed blood pressure, and high PCWP.

Therapeutic goal:
Reduce pulmonary congestion, preload, and afterload, increase cardiac output, and lower PCWP to 15 to 18 mm Hg.

Why wait for the patient to become unresponsive to traditional diuretic/digitalis therapy?

1. Forrester JS, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;295:1356-1362, 1404-1413.

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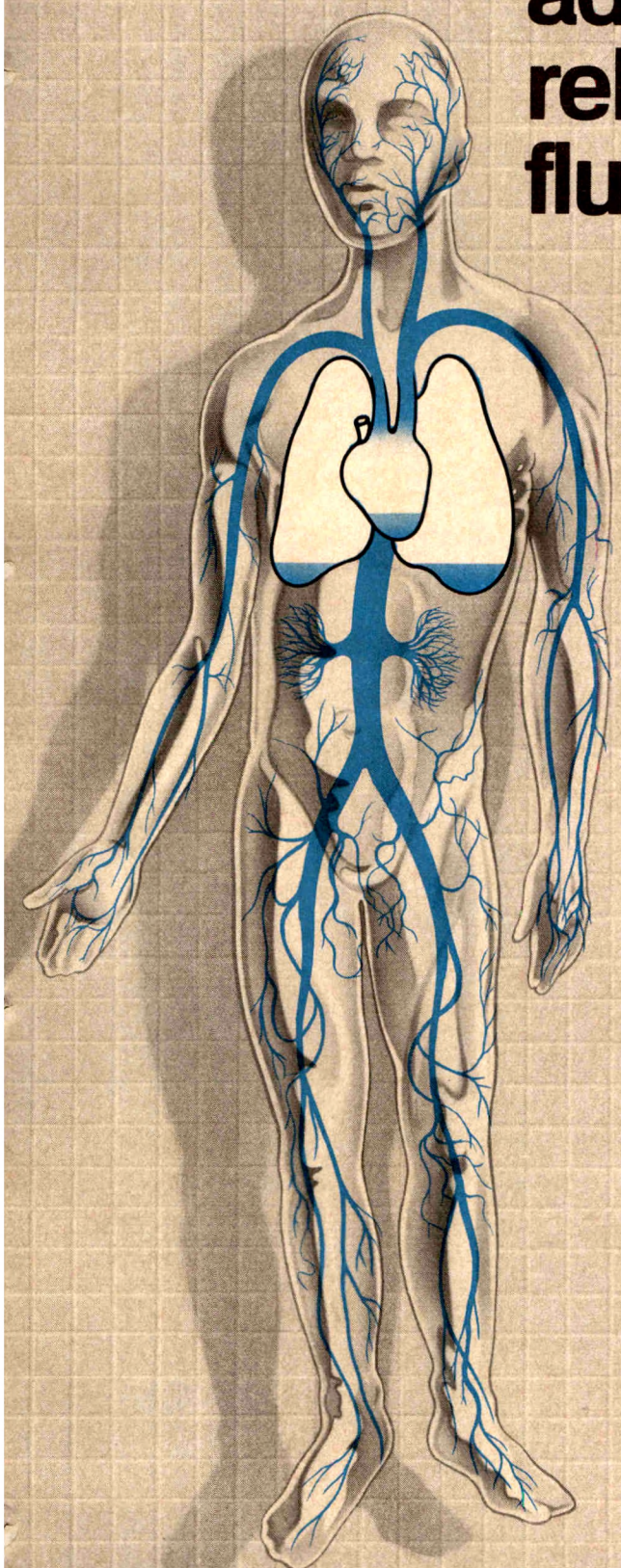
Give Tridil (nitroglycerin) adjunctively to help relieve the fluid-burdened heart



In a dose-related manner, Tridil produces dilation of both arterial and venous beds—for a therapeutic redistribution of fluid.

Suggested therapy in early CHF

If blood pressure is normal:
Tridil to reduce preload and PCWP. Diuretics to decrease fluid volume.

If blood pressure is elevated:
Tridil should be initiated immediately to decrease preload, PCWP, and blood pressure, while maintaining coronary perfusion.

Suggested therapy in late CHF

If blood pressure is normal or only moderately depressed:
Vasopressors and Tridil adjunctively, with continuous hemodynamic monitoring.

If blood pressure is significantly depressed:
Vasopressors and Tridil adjunctively to reduce preload, afterload, and PCWP. Dopamine to increase the contractility of the myocardium. PCWP should be monitored.

Use of nonabsorbing Tridilset®

Sorptive loss of Tridil may range up to 80% when infused through a conventional PVC administration set[2] To overcome this problem, administer Tridil through Tridilset administration set or Tridilset V.I.P.™ volumetric pump connector set.

The most frequent adverse reaction in patients treated with Tridil is headache. Please see the following page for a brief summary of prescribing information. Note: Tridil is a potent drug and must be diluted before infusion.

For additional information, contact the Medical Services Department, American Critical Care, division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

2. Baaske DM, et al: Administration set suitable for use with intravenous nitroglycerin. *Am J Hosp Pharm* 1982;39:121-122.

TRIDIL® (nitroglycerin) SYSTEM

American Critical Care

NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

CAUTION

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

CONTRAINDICATIONS

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinyl chloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,® an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION

(For complete information, please see Full Prescribing Information)

NOT FOR DIRECT INTRAVENOUS INJECTION

TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

HOW SUPPLIED

NDC 0094-0090-05, 25 mg-5 ml ampul. NDC 0094-0090-10, 50 mg-10 ml ampul. Each ml contains 5 mg nitroglycerin. Protect from freezing.

December 1981

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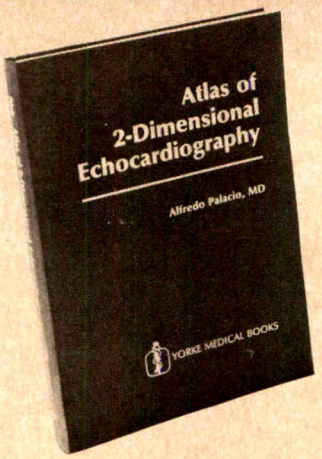

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Director of National Institute of Cardiology, Guayaquil, Ecuador
Foreword by David H. Spodick, MD, DSc
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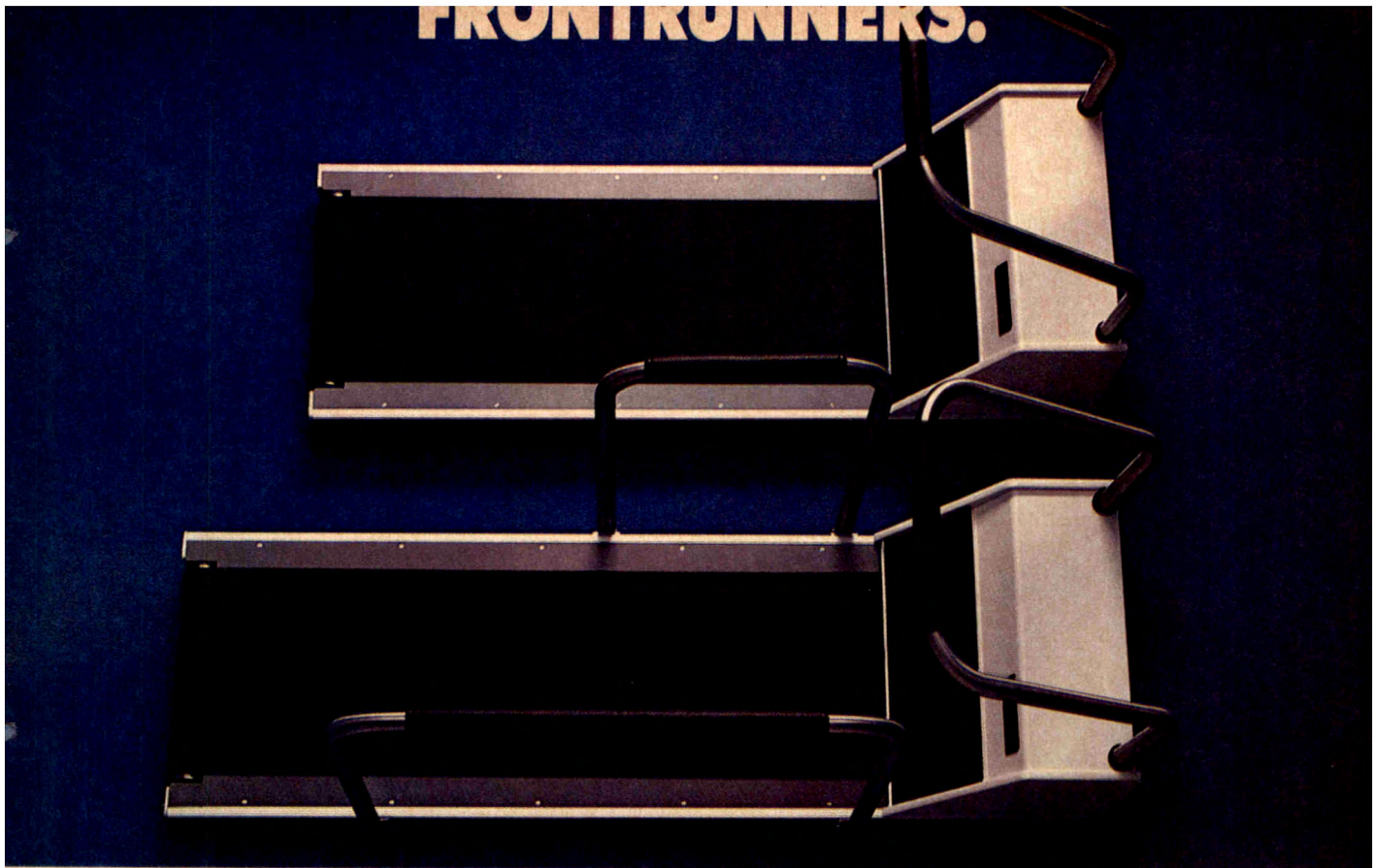

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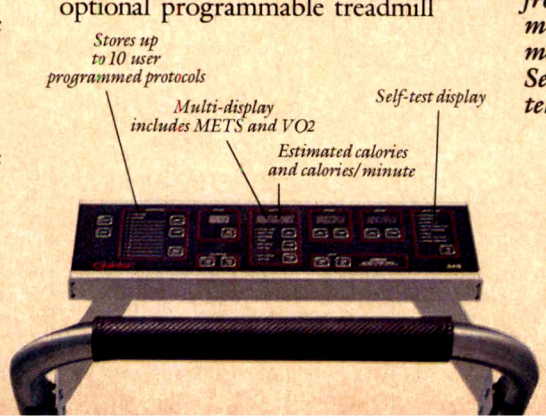

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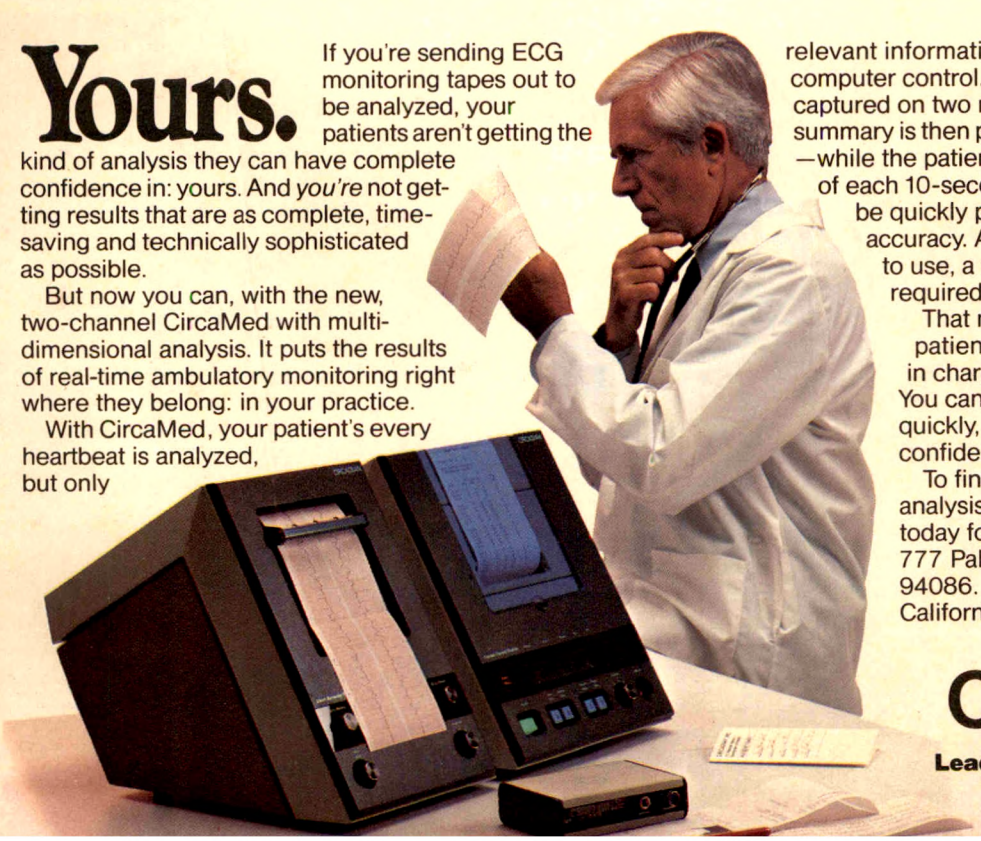

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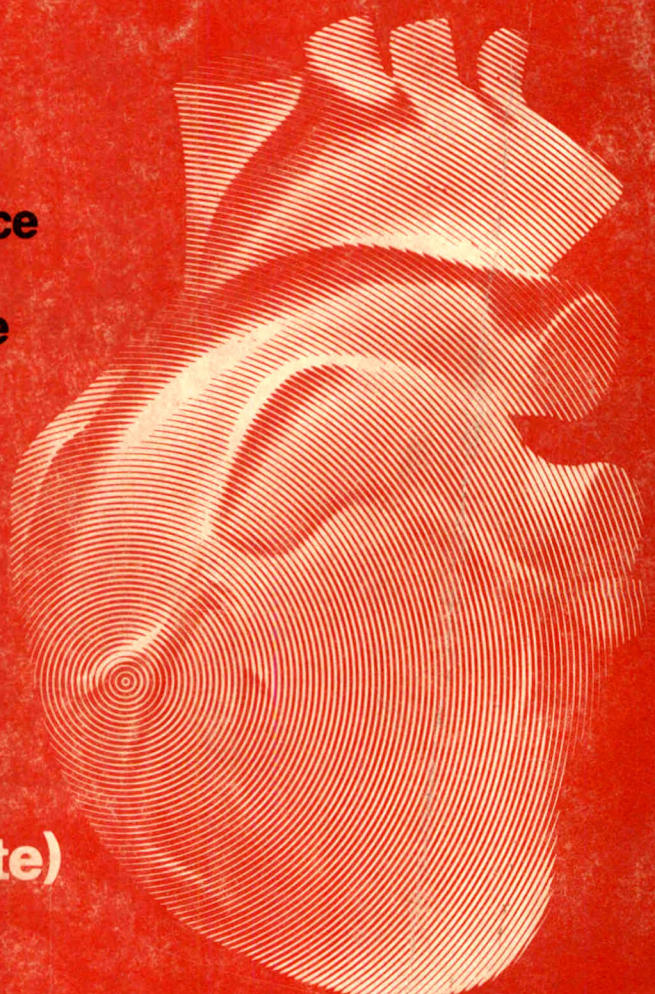

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NDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after pontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment f premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V unctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when herapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete eartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, omplete bundle branch block or other severe intraventricular conduction defects, myasthenia ravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial brillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by rogressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high entricular rate. This potential hazard may be reduced by digitalization prior to administration of uinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered oncurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence f quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or entricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or lose clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by otassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme aution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used ith caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting enal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in lasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be dministered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and etermination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are dministered. Periodic blood counts and liver and kidney function tests should be performed during ng-term therapy.

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With phenothiazines and reserpine	Additive cardiac depressive effects.
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Symposium on High-Density Lipoproteins and Coronary Artery Disease: Effects of Diet, Exercise, and Pharmacologic Intervention

Antonio M. Gotto, Jr., MD, DPhil, Guest Editor

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SYMPOSIUM ON HIGH-DENSITY LIPOPROTEINS AND CORONARY ARTERY DISEASE: EFFECTS OF DIET, EXERCISE, AND PHARMACOLOGIC INTERVENTION

Guest Editor: Antonio M. Gotto, Jr., MD, DPhil

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Symposium on High-Density Lipoproteins and Coronary Artery Disease: Effects of Diet, Exercise, and Pharmacologic Intervention

ANTONIO M. GOTTO, Jr., MD, DPhil, Guest Editor

Opening Remarks

GUNTER SCHLIERF, MD, Co-Chairman

The high-density lipoproteins (HDL) for a quarter of a century were a rather neglected member of the lipoprotein family, but during recent years have become the favorite occupation in many laboratories. Occasionally, interpretation of research findings has left solid ground and has tended to obscure the view for other facts in the area of lipids and other risk factors. The aim of this symposium is to present what is known and to discuss what is not yet known about HDL and coronary heart disease.

Figure 1 shows the lipid inputs from the gastrointestinal tract and the liver as dietary lipids or lipids of endogenous origin. A lipolytic cascade breaks down large triglyceride-rich lipoproteins to form smaller particles, which are then recognized by the liver or by peripheral cells because of certain apolipoproteins and cleared from the circulation. HDLs originate from the liver or from surplus surface materials of the large lipoproteins being broken down to accept cholesterol in the periphery and transport the steroid to the liver for degradation and excretion. It has been proposed that HDL_3, the protein-rich, lipid-poor HDL, is regenerated from HDL_2 by the action of lipolytic enzymes. Let us see how this scheme stands up in the presentations that follow.

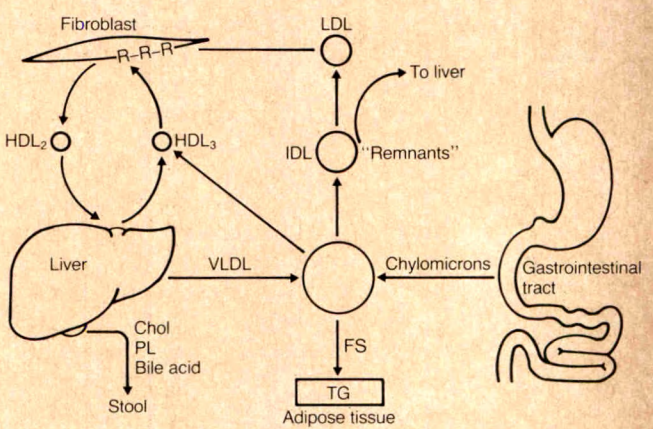

Figure 1. Lipoprotein metabolism in man. Chol = cholesterol; FS = free fatty acids; HDL = high-density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; PL = phospholipids; R-R-R = receptors; TG = triglycerides; VLDL = very low density lipoproteins.

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High-Density Lipoproteins: Biochemical and Metabolic Factors

ANTONIO M. GOTTO, Jr., MD, DPhil

The high-density lipoproteins (HDL) are the smallest of the plasma lipoprotein families and are approximately one half lipid and one half protein by weight. The major lipid constituent of HDL is phosphatidylcholine, with sphingomyelin second, followed by cholesterol and cholesteryl ester. The principal protein constituent of HDL is apolipoprotein A-I. Nascent or newly secreted HDLs, appear to be secreted by the gut, lymph and liver. The nascent HDL are converted into the native particle by the action of lecithin:cholesterol acyltransferase. The transfer of a fatty acid moiety from phosphatidylcholine to cholesterol provides a core of cholesteryl ester for HDL and facilitates formation of a stable spherical particle. Another source of nascent HDL is hydrolysis of the triglyceride-rich lipoprotein particles, which results in the formulation of HDL_2. HDL_2 are larger than HDL_3 and contain more lipid-rich particles, whereas HDL_3 are relatively protein-rich, lipid-poor, and dense. The strong inverse relation between HDL and coronary artery disease is believed to be most closely related to the HDL_2 subfraction.

A brief background on our current knowledge of the metabolism and structure of the high-density lipoproteins (HDL) will be presented as a basis for understanding the subsequent presentations.

The HDL family consists of a group of particles that contain about one half protein and about one half lipid by weight (Fig. 1).[1] We believe that these particles contain lipids, cholesteryl ester, triglyceride and unesterified cholesterol and that these water-insoluble lipids are protected by a surface monolayer consisting of apoproteins and the polar head groups of phospholipids. This monolayer along the surface then tends to interact with the aqueous exterior and maintains the lipid in a soluble state as it is transferred from the blood (Fig. 1). The major phospholipid, or lipid, constituent of HDL is phosphatidylcholine or lecithin.

There are several sources of HDL (Fig. 2). Of the apoproteins or protein components of HDL, apo A-I and apo A-II may be synthesized in the gut and also in the liver. Under certain circumstances, apo E may be secreted by the liver and may form the basis for an HDL particle. Another source of HDL is hydrolysis of the triglyceride-rich lipoproteins, either the chylomicrons derived from the gut or the very low density lipoproteins (VLDL) derived from the liver. Therefore, there are at least 4 sources of the HDL that circulate in the blood. From the liver, a particle can be secreted that contains apo E, or possibly also apo A-I, which represents a nascent form of HDL. Similar particles containing apo A-I may be secreted by the gut. These particles are called nascent HDL because, when viewed by the electron microscope, they appear as a rouleau or stacked disk. They do not have a spherical structure. To convert the nascent HDL particle to an intact HDL particle, the HDL must be acted upon by the enzyme lecithin:cholesterol acyltransferase (LCAT), catalyzing the conversion of cholesterol to cholesteryl ester.

As the core of triglyceride is hydrolyzed during hydrolysis of triglyceride-rich particles, an excess of surface constituents remains consisting of cholesterol, phospholipid and apoproteins, which are transferred to HDL, increasing its mass. Lipoprotein lipase attacks VLDL, and the surface constituents are transferred to HDL_3, which in turn is converted to HDL_2.

This phenomenon was studied in an experiment in which VLDL was treated with lipoprotein lipase under in vitro conditions. HDL_3 was also present in the test tube in the mixture. At the end of the experiment, after the lipase had attacked the VLDL, the VLDL was converted to intermediate-density lipoproteins (IDL) and HDL_3 was converted to HDL_2. On this basis, a reciprocal relation would be expected between the concentration of HDL cholesterol and VLDL triglyceride. In fact, this is the case.[2] Similarly, there is a positive correlation between concentrations of HDL cholesterol and the activity of lipoprotein lipase.

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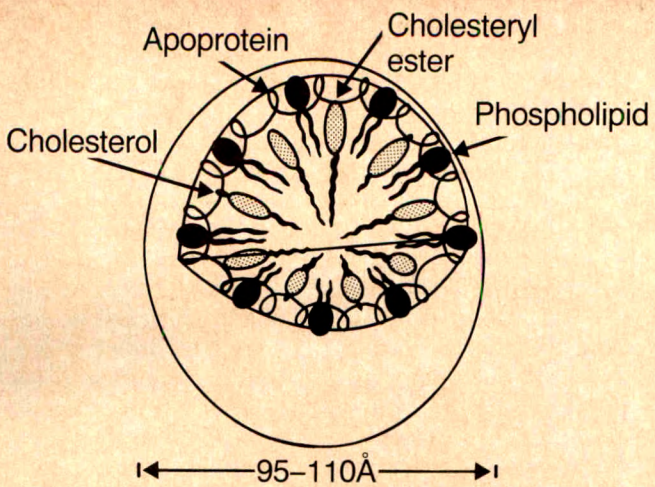

FIGURE 1. Schematic of a high-density lipoprotein particle. The protein is represented as having a helical structure and forming the outer 110 Å shell of the particle. The polar head groups of phospholipids are shown interacting with the helices of the protein. Cholesteryl esters are drawn such that the cholesterol moiety interacts with the fatty acyl chains of the phospholipids. Reprinted from Jackson et al.[1] with permission of the publisher.

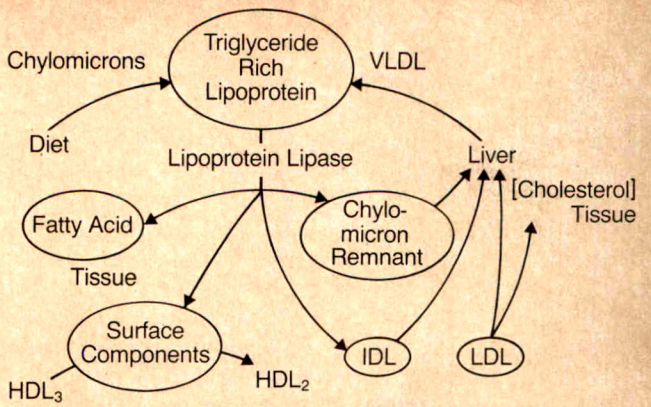

FIGURE 2. Schematic of lipoprotein metabolism. HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

It is interesting to compare differences in lipoprotein concentrations between males and females. The average concentration of VLDL is slightly higher in males. IDL is about the same. Males have a slightly higher average concentration of LDL and females a higher concentration of HDL, but by far the most striking difference is in HDL_2. Females have more than 3 times the concentration of HDL_2 than do males. Therefore, this difference in the ratio of HDL_2 to HDL_3, expressed in terms of concentration of HDL_2, is the most striking difference between lipoprotein concentrations in males and females.[3]

Table I shows apoprotein composition. The major protein component of HDL is apo A. By weight, apo A-I comprises about 46% of the total composition of HDL and apo A-II about 23%. There are 2 subfractions of HDL: HDL_2 and HDL_3. HDL_3 is relatively richer in apo A-II than is HDL_2, which has a relatively higher concentration of apo A-I. HDL also contains the apo C proteins C-I, C-II and C-III and apo D and apo E, which represent a very small proportion of HDL.

Three apoproteins form the apo A group of proteins: A-I, A-II and A-IV. A-IV appears to be made by the gut. In some species it is part of the HDL complex and in others it is found in the lipid-free state. Two apoproteins form the apo B group: B-100, the major protein of LDL made by the liver, and B-48, a minor constituent synthesized by the gut. The relative distribution of apoproteins within HDL is: A-I, 46%; A-II, 23%; C-I, 18%; C-II, 2%; C-III, 3%; D, 5%; and E, 1%. We do not have good data for A-IV. In all species studied to date, throughout evolution, apo A-I is the major apoprotein constituent of HDL.

There is a controversy about whether apo E–containing particles represent a separate, identifiable subclass within HDL. Some dietary experiments involving cholesterol feeding, particularly the feeding of egg yolks, show that concentrations of HDL and HDL_2 increase under such conditions, as does the concentration of apo E.[4] Whether this is an atherogenic or antiatherogenic effect is a matter of discussion.

Each of these apoproteins undoubtedly has 1 or more specific functions. They are involved first of all in the binding and solubilizing of lipids. Apo E is a recognition site for lipoproteins on the surface of particles. At least 1 of the isomorphic forms of apo E is recognized by receptors on the surface of hepatic cells, that is, the hepatocytes, and on the surface of other cells. Apo A-I and apo C-I are activators of LCAT, the major enzyme involved in the formation of cholesteryl ester in the blood. Apo C-II is the specific activator required for lipoprotein lipase. Some investigators have postulated that apo D may be involved in catalyzing the transfer of cholesteryl ester between HDL, LDL and VLDL,[5] but this hypothesis has been challenged.[6] There are other postulated roles, less well established and more controversial, for the other apoproteins. At least 3 major functions have been identified: the binding of lipids, service as a ligand or a recognition site for receptors on the surface of cells, and the regulation or modulation of enzymes involved in catalyzing the removal of lipoproteins from the circulation.

Within the apoproteins, there are lipid-binding sites, much as there are antigen-binding sites within antibodies. We call these regions amphipathic helices. For

TABLE I Principal Apoproteins of Plasma Lipoproteins

		Lipoprotein Class (mol %)			
Apoproteins	Chylomicrons	VLDL	IDL	LDL	HDL
A-I	3	. . .	. . .	. . .	46
A-II	3	. . .	. . .	. . .	23
A-IV	2	. . .	. . .	. . .	. . .
B-48	0.8	. . .	. . .	. . .	. . .
B-100	+	1	13	74	. . .
C-I	20	8	26	. . .	18
C-II	22	20	9	. . .	2
C-III	49	60	41	17	3
D	+	. . .	. . .	. . .	5
E	+	9	13	9	1

HDL = high-density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins.

example, in an amphipathic helix in 1 of the apo C proteins, apo C-I, there is an outer polar-face such that the poles are water-soluble; soluble amino acids are oriented toward the exterior. On the opposite end of the alpha helix is a nonpolar or hydrophobic face that interacts with the water-insoluble lipid constituents of HDL.

We have identified the crucial features necessary for lipid binding, that is, the determinants for lipid binding by the apoproteins of HDL.[7] They consist of a critical link of amino acids. We believe 20 amino acids represent the critical link, that is, a bipolar amphipathic alpha helix with a nonpolar face and a hydrophilic face. This part of the peptide or apoprotein has a relatively high degree of hydrophobicity and the ability to form an alpha-helical structure on binding to lipids.

Our hypothetical model of a lipid-binding region is called a lipid-associating peptide (LAP). We believe this peptide has certain structural analogies to apo A-I. It can be represented as a wheel because when it binds lipids and forms an alpha-helical structure, one half of the helical wheel is oriented toward the exterior. The outer part of the wheel contains the water-soluble amino acids serine and glutamic acid. This part of the helical wheel would then be water-soluble and would tend to maintain the HDL and the lipid-associating particle in a soluble state with the exterior. On the opposite side of the helix, oriented toward the interior and interacting with the lipid, are the water-insoluble amino acids tyrosine, leucine, valine and tryptophan. We have synthesized a series of such peptides and tested them.

When we tested the lipid-associating peptide LAP-20, we found that it could solubilize and bind phospholipids and cholesterol in a way very similar to that of apo A-I, the major protein of HDL. We also tested the ability of the peptide to activate the enzyme LCAT, which has an absolute requirement for apo A-I or apo C-I. On testing LAP-20, we observed activation for apo A-I and also activation by LAP-20.

In a series of synthetic peptides, we compared the ability of the peptide to bind phospholipid with its ability to activate LCAT. In every example, unless the peptide formed the amphipathic helix and could bind phospholipids, it could not activate LCAT. Not all lipid-binding peptides could activate LCAT, indicating that there are structural determinants beyond the ability to bind phospholipids that are necessary for the peptide to be able to activate LCAT.[8]

In conclusion, the apoprotein constituents have specifically defined functions, one of them being the ability to bind and solubilize the lipids; otherwise, one would not have a lipoprotein. A second function is to serve as a recognition site so that the lipoproteins may be removed from the circulation and catabolized. A third function is to regulate or modulate the enzymes involved in the catabolism of lipoprotein. By devising a series of such synthetic peptides, we may be in a position to regulate or modulate the metabolism of HDL and develop a more reasonable rationale for the treatment and prevention of atherosclerosis.

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Relation of High-Density Lipoproteins to Coronary Artery Disease

BARRY LEWIS, MD, PhD, FRCP, FRCPath

Low mean concentrations of high-density lipoprotein (HDL) cholesterol have long been recognized as a characteristic of patients with coronary heart disease, and the measurement of this fraction is a relatively strong discriminator between patients with coronary heart disease and those without. When subjects are ranked by the severity of coronary atherosclerosis determined angiographically, levels of HDL cholesterol, particularly of its HDL_2 subclass, are consistently lower in subjects with extensive disease than in those with minimal atheroma. HDL cholesterol is derived from a number of sources, mobilization from peripheral tissues being but one. Generally, longitudinal studies have confirmed that a low HDL cholesterol level is potently and independently predictive of a high risk of coronary heart disease, one exception being a study of subjects with hypercholesterolemia. Despite the strength of these epidemiologic associations, there is no evidence from experimental studies or clinical trials to establish that low HDL levels are causally important in atherogenesis.

An inverse relation between high-density lipoprotein (HDL) cholesterol levels and coronary heart disease was recognized 30 years ago.[1,2] This report reviews recent findings on this relation and lists 3 questions concerning its basis. The first is, how consistent is the inverse relation between HDL levels and coronary heart disease? Second, does this inverse relation reflect a causal interaction between this lipoprotein and atherogenesis? Third, how should such a relation influence current clinical practice?

In case-control data from a multicenter study in 4 European cities, mean HDL levels were shown to be consistently low in patients with ischemic heart disease. In all participating groups, HDL cholesterol was lower than that in matched controls, and in most or all centers, low-density (LDL) and very low density lipoprotein (VLDL) lipids were elevated (Table I). When the London data were segregated according to the patient's age, the low mean levels of HDL cholesterol were most pronounced in patients in whom ischemic heart disease developed earlier in life, and the trend did not reach statistical significance in older patients.[3]

To date, 5 longitudinal epidemiologic studies have been performed. The first of these was the study of more than 6,000 men in Tromso, Norway.[4,5] Lipoproteins were measured in persons in whom myocardial infarction subsequently developed and in twice as many matched controls. The HDL cholesterol concentration was substantially lower in those in whom ischemic heart disease developed than in the controls. Triglyceride levels were not significantly higher, whereas cholesterol levels were significantly higher in those in whom the disease developed (Table II).

In brief, similar observations were made in the Framingham study[6] and in the Israeli Heart Study (Table III).[7] However, in a prospective study in Gothenberg, Sweden, the HDL cholesterol level was not predictive of ischemic heart disease in a series of subjects with hypercholesterolemia.[8]

An informative form of case-control study was used by several groups of investigators in which patients were ranked according to the severity of the atheroma on coronary arteriograms, and the atheroma score was related to plasma lipoprotein levels.[9] A study by Jenkins et al[10] was especially attractive in that it used multivariate analysis to control for the effects of age, smoking and blood pressure. In patients with the severest atheroma, VLDL lipids were higher than in those with minimal coronary atherosclerosis; LDL cholesterol was higher and HDL cholesterol strikingly lower in those with the severest coronary artery disease (Table IV).

We used a similar design. In a consecutive series of more than 100 men who underwent coronary arteriography, we compared lipoprotein patterns in those in the lowest and highest quintiles and the middle 3 quintiles of a score of coronary atherosclerosis (Table V). HDL cholesterol was lowest in those with the severest disease. This effect was confined to the HDL_2 subclass. The mean HDL_2 cholesterol level was little more than half that of persons with minimal or no disease. There was a direct relation between LDL cholesterol level and the severity of coronary disease. The last 2 entries in Table V reflect indexes of the concentration of remnant particles in plasma, that is, of partly metabolized VLDL and chylomicrons. We found no difference in the ratio of cholesterol to triglyceride in lipoproteins with a density <1.019; this index did not discriminate between

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ABLE I Lipoprotein Cholesterol in Coronary Heart Disease, as Percentage of Age- and Sex-Matched Controls (n = 231)[3]

	London	Uppsala	Naples	Geneva
VLDL	187*	195*	128*	118*
LDL	111†	112†	130†	93
HDL	92†	84*	95	74*

* p <0.001.
† p <0.01.
HDL = high-density lipoproteins; LDL = low-density lipoproteins; DL = very low density lipoproteins.

ABLE II Tromso Heart Study: Lipids and Lipoproteins in Men Developing Coronary Heart Disease in a 2-Year Follow-Up of 6,595 Men Aged 20 to 49 Years[5]

	Cases (n = 17)	Matched Controls (n = 31)
olesterol (mg/dl)	248*	229
L cholesterol (mg/dl)	25.6*	39.4
glyceride (mg/dl)	192	165

* p <0.01.
HDL = high-density lipoprotein.

BLE III Israeli Ischemic Heart Disease Study: Mortality Per 1,000 Men in 7 Years by Quintile of Cholesterol or High-Density Lipoprotein Cholesterol Level (n ≃ 1000)[7]

	Q1	Q2	Q3	Q4	Q5
versus total cholesterol	7.6	8.2	12.6	14.2	20.2
versus HDL cholesterol	12.6	21.3	10.2	7.0	7.8
dden death versus otal cholesterol	5.4	4.4	4.5	4.3	5.6
dden death versus HDL cholesterol	5.6	11.0	4.2	3.9	2.4

HDL = high-density lipoprotein; MI = myocardial infarction; Q = ntile.

se with gross disease and those with minimal disease. nen we classified the data differently and looked at distribution of atherosclerosis in persons in the hest and lowest quintiles of the distribution of the ncentration of HDL_2 cholesterol (Table VI), patients h the highest HDL_2 cholesterol had little more than third the mean coronary artery score of persons with lowest HDL_2 cholesterol levels.

Another source of information on the relation be-een HDL and atherosclerosis is found in the longi-linal investigation of Brooks et al.[11] Using arteriog-hy of the femoral artery tree and repeating the cedure 1 year later, they quantitated the severity of eroma and calculated the rate of progression of the ease between the 2 arteriograms. Progression was ersely related to HDL cholesterol and directly to L cholesterol (Table VII). In the intervention group l controls of a regression trial in man we found a di-t relation between mean LDL cholesterol and angi-aphic evidence of progression; although an inverse

TABLE IV Lipoprotein Concentrations: Associations with Coronary Atherosclerosis Scores by Tertile (n = 41)[10]

	Lowest	Highest
VLDL triglyceride	7.1	14.8*
LDL cholesterol	6.7	16.7*
HDL cholesterol	11.4	5.1*

* p <0.05.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

TABLE V Lipoprotein Classes, Subclasses and Composition: Associations with Coronary Atherosclerosis (n = 104)[9]

	Atherosclerosis Score (Quintile)		
	1	2, 3, 4	5
HDL cholesterol (m*M*/liter	1.29	1.24	1.11*
HDL_2 cholesterol (m*M*/liter)	0.27	0.23	0.15†
LDL cholesterol (m*M*/liter)	3.00	3.45*	3.50
d <1.019 cholesterol (m*M*/liter)	1.01	1.18	1.08
d <1.019 cholesterol/triglyceride	1.08	1.08	1.07

* p <0.05.
† p <0.01.
d = density; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

relation between HDL and progression was seen it was weaker and not significant.

All of these studies show a connection between HDL and the atherogenic process; however, in some situations HDL does not show such a relation. In the collaborative study in which colleagues in Italy, Switzerland and Sweden and our group in London compared, by identical methods, the lipoprotein concentrations in normal persons of both sexes and different ages,[3] levels of both LDL and VLDL lipids were higher in the relatively high coronary heart disease areas in Sweden and in the United Kingdom than in Switzerland and in Italy. Therefore, an association exists between the mortality from ischemic heart disease in these 4 industrialized European cities and these lipoproteins. However, there were virtually no differences in HDL cholesterol. To the extent that interpopulation differences in coronary heart disease can be attributed to lipoprotein-mediated risk, such differences must be associated with LDL and perhaps with VLDL, but these interpopulation differences in coronary heart disease rates could not be attributed to differences in HDL cholesterol levels.

The answer of the second question concerning a causal relation between HDL and atherogenesis is unknown. As discussed by Gotto in this symposium, HDL enters plasma as a discoidal particle and is derived from both the small intestine and the liver. Its subsequent metabolism is considerably more complex, and for discussion we will isolate a few aspects. Under the influence of the enzyme lecithin-cholesterol acyltransferase (LCAT), the free cholesterol of nascent HDL is largely converted to cholesteryl ester, which comes to form the core of a spherical HDL particle.

TABLE VI Frequency of Coronary Artery Disease Related to Distribution of HDL_2 Cholesterol (n = 104)[9]

	HDL_2 Cholesterol (Quintile)		
	Lowest	Highest	p
Coronary score	28.3	10.8	<0.002
Mean number of stenoses	5.7	2.4	<0.002
Patients with stenoses (n)	20	13	<0.01

TABLE VII Femoral Atherosclerosis Progression Rate[11]

	Relation	F
α HDL	Inverse	7.79
α LDL	Direct	5.68

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE VIII Hyperalphalipoproteinemia and Cholesterol Kinetics[14]

	Patients With Hyperalphalipo-proteinemia	Control Subjects
Cholesterol in pool A (g/70 kg)	21.0	28.7
Cholesterol in pool B (g/70 kg)	21.5*	51.5
Tissue cholesterol pools (g/70 kg)	34.6†	69.9
Cholesterol turnover (mg/kg/d)	9.4†	15.1

* $p < 0.01$.
† $p < 0.05$.

HDL cholesterol is derived not only from primary secretion by the liver and gut but also from other sources. Additional cholesterol transfers to HDL from extrahepatic cells, subsequently being converted by LCAT to cholesteryl ester. This cholesteryl ester may reach the liver, at least in part, by transfer through a specific transfer protein to triglyceride-bearing lipoproteins. These lipoproteins undergo further metabolism and are ultimately metabolized, at least in part, by the liver, returning their cholesterol to this organ. Therefore, HDL may play a role in initiating the uptake of cholesterol from peripheral cells rather than in transporting it to the liver for excretion in the bile.

Some HDL cholesterol, perhaps a considerable portion, is derived from triglyceride-rich lipoproteins (VLDL and chylomicrons) within the circulation, as a result of the action of lipoprotein lipase.

A third source of HDL cholesterol is the cholesterol derived from peripheral cells. The upshot of these processes is that HDL cholesterol is derived from multiple sources. Hence, an increase in the concentration plasma of HDL cholesterol does not establish that reverse cholesterol transport has been enhanced. Microsomal inducing agents, for example, increase HDL cholesterol probably by stimulating its hepatic secretion, and factors that activate lipoprotein lipase, such as certain drugs, probably increase HDL cholesterol by promoting transfer of cholesterol to HDL from VLDL and chylomicrons.

Some evidence suggests that high HDL cholesterol levels reflect an increase in reverse cholesterol transport. Miller et al[13] investigated the relation between levels of HDL cholesterol in plasma and the exchangeable pools of cholesterol in extravascular spaces. In this small study, remarkably significant inverse relations were found between the amount of HDL cholesterol in plasma and the amount of exchangeable cholesterol in the tissues, findings certainly compatible with a role of HDL in centripetal transport. Evidence also exists that HDL or particles that contain HDL apoproteins and phospholipids serve as acceptors of cholesterol when cells are incubated in their presence.

In persons who have inherited high levels of HDL, the exchangeable pools of cholesterol, especially the slowly exchanging pool, are far smaller than the pools in control subjects (Table VIII).[14] Coronary heart disease appears to be rare in such persons.

The relation between HDL metabolism and the metabolism of other lipoproteins is complex, and it is difficult to study variables in man that influence any single lipoprotein in isolation. For example, HDL levels are strongly correlated with the fractional catabolic rate of VLDL and with the activity of lipoprotein lipase in adipose tissue. The rate of production of VLDL is related, for obscure reasons, to the rate of synthesis of HDL. It is difficult in the intact organism to isolate the determinants in the consequences of changes in any 1 lipoprotein.

In summary, HDL does function as a circulating acceptor of cholesterol from peripheral cells. There is good evidence that HDL initiates the reverse transport of cholesterol from the periphery back to the liver. HDL or a subclass of HDL that contains apo E competes with LDL for receptor-mediated binding by cells, and thereby may reduce the uptake of LDL cholesterol by peripheral cells.

What are the implications of these findings for clinical practice? We have no evidence that interventions that change HDL concentration influence the risk of coronary heart disease. We do not have animal models; we do not have controlled trials analogous to those that have provided evidence for the beneficial effect of the reduction of total plasma cholesterol. A reasonable view is that in persons who have low HDL concentrations together with one or another form of hyperlipidemia, an optimal treatment should normalize all lipoprotein abnormalities.

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High-Density Lipoproteins: Epidemiologic Profile and Risks of Coronary Artery Disease

WILLIAM B. KANNEL, MD, MPH

The lipid-atherogenesis connection has undergone an evolutionary metamorphosis from a focus initially on serum total cholesterol, subsequently on other lipids, then on the lipoproteins that transport them, and now on the distribution of cholesterol in the low-density lipoproteins (LDL), high-density lipoproteins (HDL) and very low density lipoproteins. It is now established that the relation of serum total cholesterol to coronary heart disease (CHD) derives chiefly from the atherogenic LDL component, and that level of HDL cholesterol is inversely related to risk. The protective effect of HDL is at least as strong as the atherogenic effect of LDL and is independent of lipids and other risk factors. Every change of 10 mg/dl in the HDL cholesterol level is associated with a 50% change in risk. At any level of serum total cholesterol, risk varies widely, depending on the LDL/HDL ratio. A serum total cholesterol/HDL ratio of 5.0 is associated with average risk; optimal ratios, around 3.5, correspond to half the standard risk. Further refinements in the lipid profile may be possible because there are several HDL and LDL subfractions with different atherogenic potential probably related to their apoprotein makeup. Only weak and inconsistent relationships of stroke and peripheral arterial disease to serum cholesterol and its lipoprotein fractions have been found, although there is the expected inverse relation to HDL cholesterol. An inverse relation of LDL level to stroke in women, and in men a possible excess mortality at very low serum cholesterol values attributed to colon cancer, have been reported.

This report evaluates high-density lipoprotein (HDL) from an epidemiologic standpoint and, in particular, focuses on its role as part of a lipid profile for predicting coronary disease and also as an ingredient of a cardiovascular risk profile. It is widely recognized that atherosclerosis is a multifactorial process, and blood lipids appear to play a central role. The concept of lipid atherogenesis has undergone an evolutionary metamorphosis from an initial focus on the serum total cholesterol, to a focus on the other lipids, and then to the lipoproteins that transport them. The 2 lipoproteins described by Gofman et al, the beta or low-density lipoproteins (LDL) and the pre-beta or very low density lipoproteins (VLDL), are clearly related to coronary incidence. There is also a metabolic metamorphosis of the lipid particles that occurs as VLDL is converted to LDL via transient IDL remnants. In this process there is a progressive enrichment with cholesterol, and it is now believed that the LDL fraction is the atherogenic component and that the HDL fraction may be involved in cholesterol removal from the tissues.

We have learned from Drs. Gotto and Lewis in this symposium that the frontiers of lipid atherosclerosis research now encompass the apoprotein makeup of these lipoproteins and the subfractions of HDL and LDL that may be more specifically atherogenic or protective. The recent evidence continues, however, to incriminate cholesterol, but it also indicates that we need to consider the distribution of the cholesterol in the lipoproteins and, furthermore, that we must take into account other factors that injure the endothelium, affect its permeability, influence the extent of smooth muscle proliferation and fibrosis, and affect platelet aggregation.

Epidemiologic studies have now firmly established that there is indeed a strong, prospective and independent association between the serum total cholesterol concentration and the occurrence of coronary heart disease (CHD).[1–3] This relationship has been demonstrated in both sexes. It has been demonstrated for all clinical manifestations of CHD. Over the usual range of values that the laboratory designates within normal limits, there is a 5-fold range of risk. We have identified no critical values where normal leaves off and abnormal begins. It would appear that the higher the level, the

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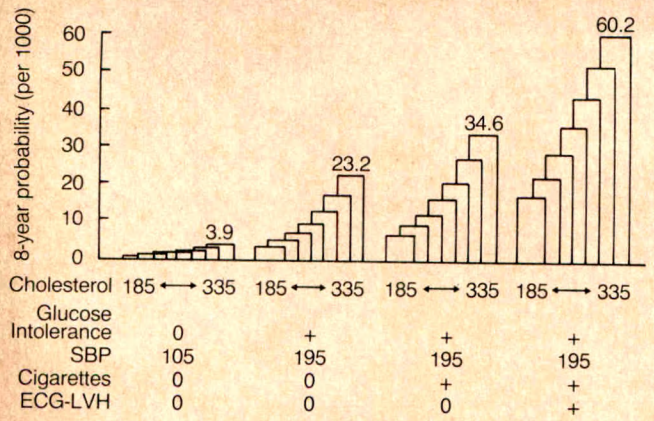


*Framingham study, 18-year follow-up (Monograph No. 28); 35-year-old men.

FIGURE 1. Risk of cardiovascular disease according to serum cholesterol at specified levels of other risk factors. ECG-LVH = electrocardiographic evidence of left ventricular hypertrophy; SBP = systolic blood pressure. From the Framingham study, 18-year follow-up (Monograph No. 28); 35-year-old men. The Framingham Study. An epidemiologic investigation of cardiovascular disease. Sect. 28. The probability of developing certain cardiovascular diseases in 8 years at specified values of some characteristics. Daniel McGee DHEW Publication No. (NLH) 74-618, 1973.

TABLE I Risk of Coronary Heart Disease According to Cholesterol-Lipoprotein Fractions*

Lipoprotein-Cholesterol Fraction	Standardized Regression Coefficients			
	Univariate		Multivariate†	
	Men	Women	Men	Women
LDL cholesterol	0.210‡	0.254‡	0.251‡	0.189
HDL cholesterol	−0.531‖	−0.554‖	−0.572‖	−0.479§
VLDL cholesterol	0.103	0.234‡	0.002	0.081

* Framingham study, 4-year follow-up; subjects 50 to 80 years old.

† Multivariate variables: other lipids, age, systolic blood pressure, glucose, cigarettes, electrocardiographic evidence of left ventricular hypertrophy.

‡ $p < 0.05$.

§ $p < 0.01$.

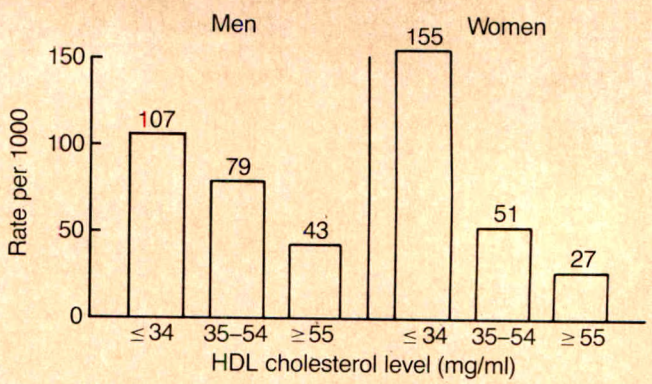
‖ $p < 0.005$.

From: Kannel WB, Gordon T, Castelli WP. Role of lipids and lipoprotein fractions in assessing atherogenesis. The Framingham Study. Prog Lipid Res 20: 339–348, 1981.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

greater the risk; the lower the level, the less the risk of coronary disease.

We now also know that the impact of cholesterol diminishes with advancing age; beyond age 65 years it is difficult to show any relation at all. We also recognize that cholesterol-related risk is markedly influenced by the coexistent risk factor levels, although at any level of other risk factors there is an independent relationship of CHD to serum total cholesterol value (Fig. 1). Thus, any level of cholesterol, high or low, has a very different significance, depending on the mix of the other risk factors. Furthermore, we now understand that it is also important to determine how this total cholesterol is distributed in the LDL and HDL fractions (Table I). It



†Framingham study, exam 11; men and women 50–79 years old. Trends significant at $p < .01$.

FIGURE 2. Incidence of coronary heart disease by high-density lipoproteins (HDL) cholesterol level.

TABLE II Relative Risk of Developing Clinical Coronary Heart Disease in 4 Years According to Specified Concentrations of High-Density Lipoprotein Cholesterol and Low-Density Lipoprotein Cholesterol*

HDL Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)		
	100	160	220
25	1.2	1.9	2.9
55	0.4	0.6	1.0
85	0.1	0.2	0.3

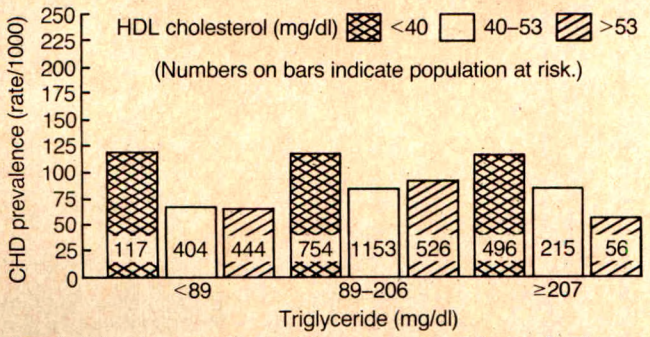
* Men 50 to 70 years old with systolic blood pressure of 135 mm Hg.

From: Kannel WB. Coronary Risk Handbook. HDL cholesterol in persons over 50. The Framingham Study. 1978.

HDL = high-density lipoproteins; LDL = low-density lipoproteins.

is now clear that the positive relationship of the serum total cholesterol to CHD incidence derives mainly from the LDL cholesterol component. Thus, there is a strongly positive relationship between LDL cholesterol and the risk of coronary events (Table II). HDL cholesterol is inversely related to coronary incidence (Fig. 2), consistent with its purported role in removing cholesterol from the tissues. VLDL cholesterol and its triglyceride apparently make no independent contribution to risk, although it is related to coronary incidence taken alone in the univariate case. Even at high triglyceride values there is the expected inverse relationship of HDL to CHD incidence, while at low HDL values, there is no relationship of triglyceride to coronary incidence (Fig. 3).

On the basis of multivariate formal statistical analysis (as measured by the size of the multivariate coefficient), the protective effect of HDL appears to be greater than the atherogenic effect of LDL cholesterol. This has been shown so far only for the elderly Framingham cohort and needs to be corroborated in younger persons. Nevertheless, the evidence suggests that the HDL influence is at least as strong as the LDL influence. For every 10-mg increment in HDL, there is about a 50% change in coronary risk, a very powerful effect. Both the LDL and HDL effects are independent of each other,



*Pooled data from Cooperative Lipoprotein Phenotyping Studies. Trend of CHD on lipid HDL $p < 0.01$; triglyceride NS.

FIGURE 3. Prevalence of coronary heart disease (CHD) by levels of triglyceride and high-density lipoprotein (HDL) cholesterol in men aged 50–69 years. NS = not significant. Pooled data from Cooperative Lipoprotein Phenotyping Studies. From Castelli WP, Doyle JT, Gordon T, Hames CG, Hjortland MC, Hulley SB, Kagan A, Zukel WJ. HDL-cholesterol and other lipids in coronary heart disease: the Cooperative Lipoprotein Phenotyping Study. Circulation 1977;55:767–772. Reproduced with permission of the publisher.

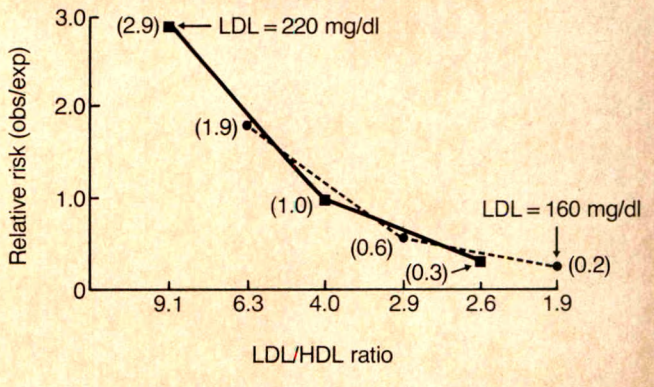
TABLE III Efficiency of Cholesterol-Lipoprotein Ratios Composed of Low-Density Lipoprotein Cholesterol, High-Density Lipoprotein Cholesterol and Total Cholesterol*

	Likelihood Ratios	
	Men	Women
Ratios		
Low-density lipoprotein/high-density lipoprotein cholesterol	17.54†	17.97†
Total/high-density lipoprotein cholesterol	16.76†	21.41†
Linear combinations		
Low-density lipoprotein cholesterol + high-density lipoprotein cholesterol	20.06†	18.01†
Total cholesterol + high-density lipoprotein cholesterol	18.56†	20.58†

* Framingham study and 8-year follow-up; men and women, 50 to 80 years old.
† $p < 0.001$.

of all the other lipids, and of all the other major risk factors. Also, at any level of serum total cholesterol (or of LDL cholesterol), the CHD risk varies widely, depending on the ratio of LDL to HDL (or the ratio of total cholesterol to HDL). Both at low LDL values or high LDL values, risk is markedly influenced by the LDL/HDL ratio (Fig. 4).

Fortunately, a comparison of ratios made up of LDL to HDL with those made up of the more practical total cholesterol to HDL reveals risk gradients that are similar (Table III). Also, there is no particular benefit to making linear combinations of LDL and HDL compared with ratios based on likelihood ratio statistics. The ratio of the 2 lipoprotein-cholesterol fractions seems to provide as efficient a discrimination of cases from noncases (Table III). Hence, the total cholesterol/HDL ratio will efficiently identify patients who are at increased risk over the usual range of total cholesterol values. A ratio of about 5 is the average or standard risk. One of about 3.5 is about half the standard risk and can be considered optimal, whereas a ratio of 10 is double the standard risk, and a ratio of about 20 is 3 times the average risk. These are ratio numbers easy to remember.



†Framingham study, men 50–70 years old.

FIGURE 4. Relative risk of coronary heart disease in 4 years as a function of the low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio at high and low LDL levels. obs/exp = observed/expected.

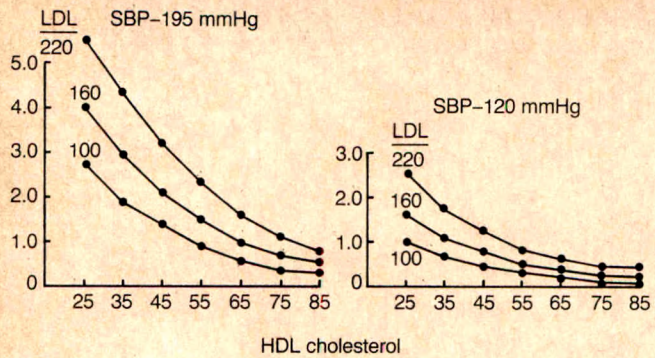
TABLE IV Likelihood Ratios for Risk of Coronary Heart Disease According to Lipid Profiles*

	Likelihood Ratios	
HDL + LDL Cholesterol	Men	Women
With triglyceride	18.90†	24.73†
Without triglyceride	18.66†	23.70†

* Framingham study, 7-year follow-up; subjects 50 to 80 years old.
† $p < 0.001$.
From Kannel WB, Gordon T, Castelli WP. Role of lipids and lipoprotein fractions in assessing atherogenesis. The Framingham Study. Prog Lipid Res 20: 339–348, 1981.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

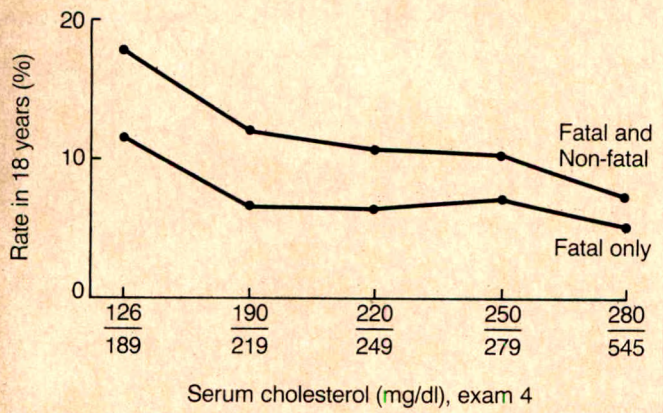
Adding triglyceride to the HDL and LDL lipid profile (Table IV) appears to do nothing to improve the efficiency of the estimation of risk. The combination of HDL, LDL and blood pressure exerts a very powerful influence on risk (Fig. 5). At any level of HDL, risk increases with LDL, and at any level of LDL and blood pressure, risk is markedly influenced by HDL. Consistent with the findings of Glueck in this symposium, persons with very high HDL values can tolerate a lot of variation in LDL and blood pressure with relative impunity (Fig. 5). Risk in persons with low HDL cholesterol levels is high and greatly influenced by coexistent LDL and blood pressure.

Some further refinements in lipid profiles may be forthcoming shortly. Several subfractions of HDL and LDL with different apoprotein makeups have the potential to further improve current lipid risk profiles. However, no prospective epidemiologic data exist to test this hypothesis.



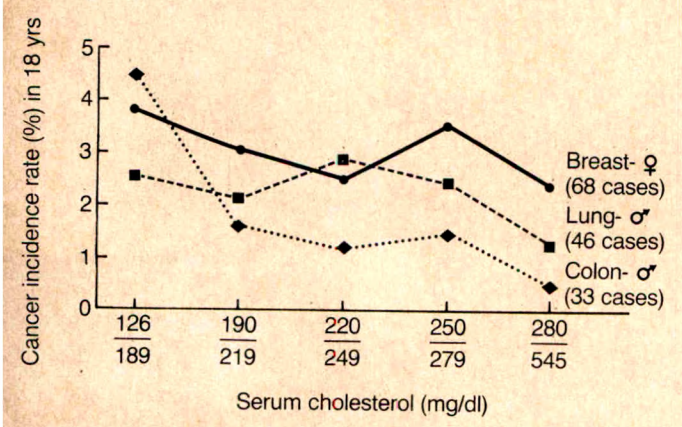
*Framingham study, male subjects 50–70 years old.

FIGURE 5. Relative risk of coronary heart disease according to high-density lipoproteins (HDL), low-density lipoproteins (LDL) and systolic blood pressure (SBP). From Kannel WB. Can we prevent heart attacks? Cardiovascular Diseases: Clinical Update. Health Learning Systems [monograph] [in press]. Reproduced with permission of the publisher.



*Framingham study, men 35–69 years old.

FIGURE 6. Cancer mortality and morbidity (age-adjusted). From Feinleib M. Summary of a workshop on cholesterol and noncardiovascular mortality. Prev Med 1982;11:360–67. Reproduced with permission of the publisher.



*Framingham study, age 35–69 years old.

FIGURE 7. Age-adjusted incidence of breast cancer in women and lung and colon cancer in men. From Feinleib M. Summary of a workshop on cholesterol and noncardiovascular mortality. Prev Med 1982;11: 360–367. Reproduced with permission of the publisher.

Another feature that deserves further investigation is the relationship of these lipid profiles to other clinical atherosclerotic manifestations. There is sparse and inconsistent information on the relationship of lipid profiles to other atherosclerotic events such as stroke, cardiac failure or occlusive peripheral arterial disease. For HDL cholesterol, almost all the risk gradients are negative, consistent with a beneficial effect.

However, for LDL, there is a paradoxical effect of a strong inverse relationship to stroke incidence that deserves further investigation. Consistent with this, the Japanese have also reported an inverse relationship of stroke to total cholesterol. VLDL cholesterol does not seem to exert much of an influence of any sort on any of the other atherosclerotic events.

At the same time that the relationship of cholesterol to CHD mortality has been clarified, an interesting problem has arisen of an inverse relationship of serum total cholesterol to overall mortality and, in particular, to colon cancer mortality, that requires further investigation (Fig. 6 and 7). The findings are inconsistent and paradoxical, because they can be demonstrated only for men. Moreover, an examination of the relationship of diet to colon cancer indicates that a high-fat diet seems to predispose. This tends to discredit a causal relationship between low cholesterol and colon cancer.

Nevertheless, the aforementioned relationship to overall and noncardiovascular mortality raises the question of what an optimal cholesterol value is. Optimal values for prevention of coronary disease and atherosclerosis are probably 140 to 180 mg/dl. Those in the 180- to 200-mg/dl range also have a favorable overall mortality risk and a good health status. Total cholesterol values >200 mg/dl generally appear to be suboptimal in regard to cardiovascular health.

So far, the results of trials to reduce coronary risk by either drugs or diet have been rather unimpressive. This may well be because we have not started the investigation early enough and have not continued long enough; nor have we achieved a substantial enough reduction in the lipid values, and we may not have achieved an improvement in the LDL/HDL ratio. Fortunately, the measures advocated to prevent CHD—such as weight reduction, smoking abatement, exercise, correction of diabetes, and even moderate alcohol intake—also have a favorable effect on the HDL value.

Obviously, we need to learn more about the role of the lipid profile in promoting and predicting coronary disease and in evaluating the efficacy of treatment. However, recognizing the incompleteness of the state of knowledge is no excuse for failing to apply more effectively what is known.

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Influence of Exercise on High-Density Lipoproteins

Lt. Col. GEORGE O. COWAN, MB, FRCP, RAMC

The effects of an intensive rehabilitation course on plasma high-density lipoprotein (HDL) levels were studied in 40 men, aged 29 to 56 years, with ischemic heart disease. The exercise consisted of aerobic activities that induced up to 80% of the maximal heart rate during three 20-minute periods daily for 5 days a week; the program lasted 3 weeks. Significant increases were found in the levels of HDL and HDL_2 and their ratios to total plasma cholesterol. These changes were similar in nonsmokers of cigarettes and in men who gave up or reduced smoking during the course and contrasted with negligible changes in those who continued to smoke.

This study reports the results of changes in high-density lipoprotein (HDL) cholesterol during a cardiac rehabilitation program. In the American army, 15% of the soldiers are grossly overweight, perhaps because the standard mess hall diet contains more than 4,000 kcal/day. At Fort Eustis, Virginia, 100 soldiers were ordered to restrict themselves to 1,500 kcal/day, and over 10 weeks they achieved an average weight loss of 20 pounds, with a decrease in blood pressure and triglyceride levels as well.

Great Britain still has one of the world's highest incidences of ischemic heart disease, and the risk gets worse the further north one goes. British army soldiers have the same overall incidence as the general male population of Britain. However, the differences uncovered through social class analysis of our figures by Lynch and Oelman[1] are perhaps surprising in that corporals and enlisted men have twice the standard mortality ratio from sudden death from myocardial infarction, and Sandhurst or West Point officers, for example, have one third of the standard mortality ratios. This finding presumably reflects many aspects of their very different lifestyles: their habits and upbringing in terms of diet, their habits and philosophy of exercise and leisure pursuits, the wide disparity in smoking habits and perhaps also hereditary and economic factors. In this study, bias for age distribution and geographic origin within the United Kingdom has been statistically removed.

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Methods

When the Queen Elizabeth Military Hospital in Woolwich, London, was opened in 1977, it was decided to devote a major effort to identifying and treating servicemen with coronary artery disease. Equipment for exercise electrocardiographic testing and thallium-201 myocardial perfusion scanning was installed, and the effort was coordinated by the establishment within the hospital of the joint services school of remedial gymnasts who, it was planned, would provide the expertise and motivation necessary to promote vigorous physical exercise in the rehabilitation of men who have suffered the severe physical and emotional trauma of myocardial infarction and who were well aware that this jeopardized their military career.

The cardiac rehabilitation course, therefore, had 3 aims: restoration of physical fitness, psychological repair and secondary prevention. All British army men are required to pass a test of fitness twice a year over a 3-mile (4.8-km) course in 26 to 30 minutes. We intended that subjects with ischemic heart disease would achieve the normal target for their age at the end of the course. Psychological repair comes through increased physical fitness and confidence and also through a very strong sense of group identity fostered by evening discussions. The third aim, secondary prevention, is unproved. However, we have now treated more than 300 men, and we know that the first 2 aims can be achieved safely. What I want to report is perhaps a hopeful aspect in relation to the aim of secondary prevention.

The cardiac rehabilitation course actually works in the following way. Men were assembled in groups of eight 6 to 8 weeks after myocardial infarction or coronary artery bypass surgery. Some men do 2 courses, 1 after the infarction and 1 after surgery. A few are included who have angina of effort only and have not had myocardial infarction. The group is supervised by 2 remedial gymnasts, and in many periods of the exercise, each patient is accompanied by a gymnast student. We specifically avoid having physicians present during

the exercise. The gymnasts are in control. The course lasts 3 weeks, with weekends off, making 15 days of progressive exercise.

On the first day a safe work load for each patient is determined by use of the Bruce treadmill protocol for exercise electrocardiographic testing and is based on, for the first week, 70% of the maximal heart rate; for the second week, 75%; and for the third week, 80%. We determined these figures empirically to start with, but in practice they are safe and effective. Beta-adrenergic blocking drugs are discontinued during the course. The exercise program is obviously progressive and is based on the plan of 3 periods each day of 20 minutes, building up to 40 minutes during which the target heart rates are achieved. The exercise program varies considerably according to the time of year and the taste of the group, but it is all aerobic exercise and contains a mix of jogging, short trot-sprints, calisthenics, swimming, cycling and brisk walking. Lectures and films on the etiology of ischemic heart disease and on diet and smoking are included.

Subjects are advised at the start of the course about the so-called prudent diet, low in animal fat and refined carbohydrates, and meals of this type are made available in the dining room, but the men are not compelled to avoid imprudent items. Alcohol is not available during the weekdays, of the course, but it is assumed that many men include it in their weekend relaxation. No significant changes were recorded in body weight or skinfold thickness during the course. The whole program is based on strict control of pulse rate, monitored by the subjects themselves and by the gymnasts.

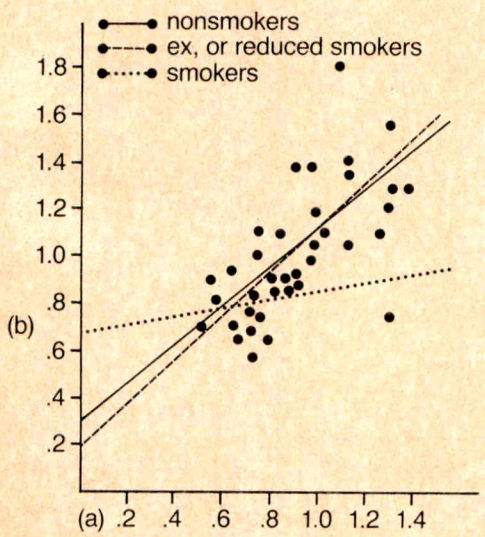

FIGURE 1. High-density lipoprotein levels (**a**) before treatment and (**b**) after treatment (in mmol/liter).

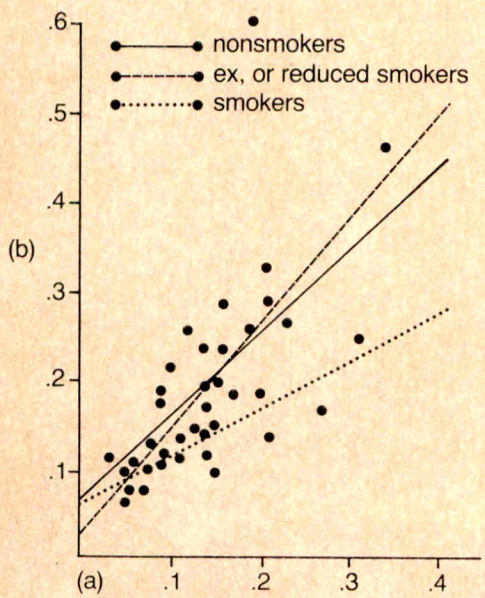

FIGURE 2. High-density lipoprotein$_2$ levels (**a**) before treatment and (**b**) after treatment (mmol/liter).

Results

The results of our study in 40 men aged 29 to 56 years (mean 40.6) compare fasting blood lipids taken on day 2 to those taken on day 17. HDL cholesterol increased from a mean of 0.87 to 0.95 mmol/liter (Fig. 1). HDL_2 increased from a mean of 0.14 to 0.19 mmol/liter (Fig. 2), and the ratios of HDL to cholesterol (Fig. 3) and HDL_2 to cholesterol (Fig. 4) also showed highly significant increases. The HDL_2 to total cholesterol mean increased from 0.026 to 0.039. Therefore, whichever way these data are analyzed statistically (Table I), these differences are all highly significant.

We wanted also to determine how cigarette smoking affected the results. Of the 40 men in the group, 19 did not smoke, 15 either stopped or reduced smoking markedly during the course and 6 continued to smoke as before. The separate regression lines show that nonsmokers and exsmokers had a significant increase in HDL and that smokers had virtually no change at all (Fig. 5). For HDL_2, the same applies. There was some increase in HDL_2 in the smokers, but it was not nearly as great as that in the other groups (Fig. 6). Again, statistical analysis shows that only those who continued

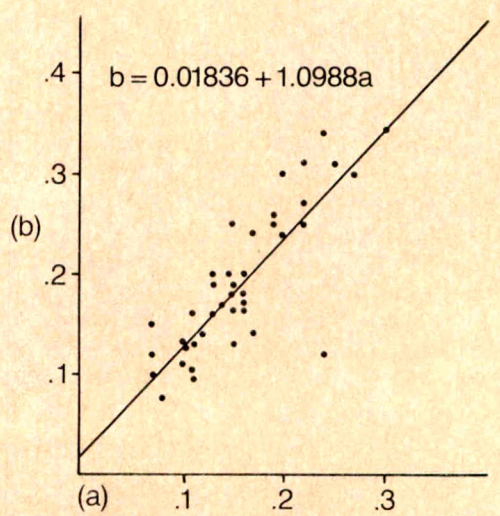

FIGURE 3. Ratio of high-density lipoprotein to cholesterol (**a**) before treatment and (**b**) after treatment.

TABLE I Variation in Plasma High-Density Lipoproteins, HDL_2 and Ratios to Cholesterol Before and After Cardiac Rehabilitation Course (n = 40)

	Wilcoxon Test	Correlation Coefficient	ANOVA	Ratio Test	% Change
HDL	XX*	XXX	XXX	XX	+43.23
HDL_2	XXX†	XXX	XXX	XXX	+38.34
HDL cholesterol	XXX	XXX	XXX	XXX	+66.50
HDL_2 cholesterol	XXX	XXX	XXX	XXX	+47.60

* XX = rejection at 1.0%, $p < 0.01$.
† XXX = rejection at 0.1%, $p < 0.001$.
ANOVA = analysis of variance; HDL = high-density lipoprotein.

to smoke had no significant change, and the differences between the 3 subgroups are all highly significant (Table II).

It is well established that in the general asymptomatic male population of developed countries, plasma HDL is highest in the most physically active. It is equally well established that HDL and HDL_2 levels correlate strongly with the incidence, severity and mortality from coronary artery disease. Huttunen et al[2] studied 18 male coronary patients exercised to 70% of maximal oxygen uptake 3 times a week for 20 to 40 minutes over a 3-month period and found a 15% increase in total HDL, from a mean of 1.02 to 1.18 mmol. Streja and Mymin,[3] in a cardiac rehabilitation program, studied 32 sedentary men with coronary artery disease over a 13-week period, exercising them by jogging 2.8 km 3 times a week, and found only very slight increases in HDL.

Our study of 40 men with coronary artery disease shows that they may be exercised vigorously. For instance, on the Thursday of the third week, it is common for men on the course to cover 12 miles on foot with a mixture of running and walking, to swim 30 lengths of

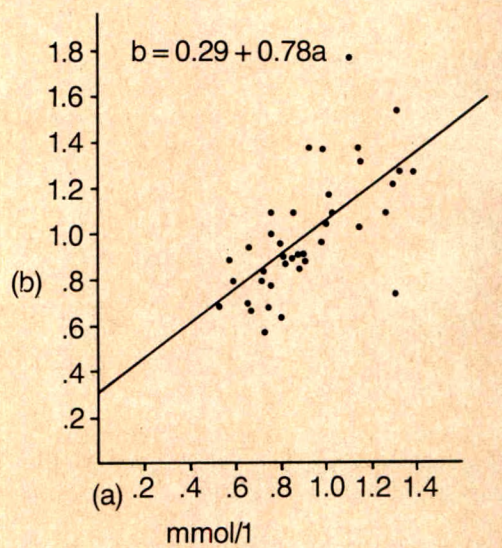

FIGURE 5. High-density lipoprotein levels (**a**) before treatment and (**b**) after treatment.

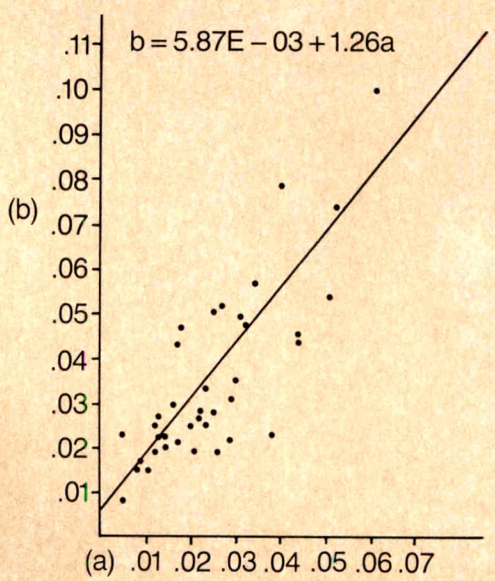

FIGURE 4. Ratio of high-density $lipoprotein_2$ to cholesterol (**a**) before treatment and (**b**) after treatment.

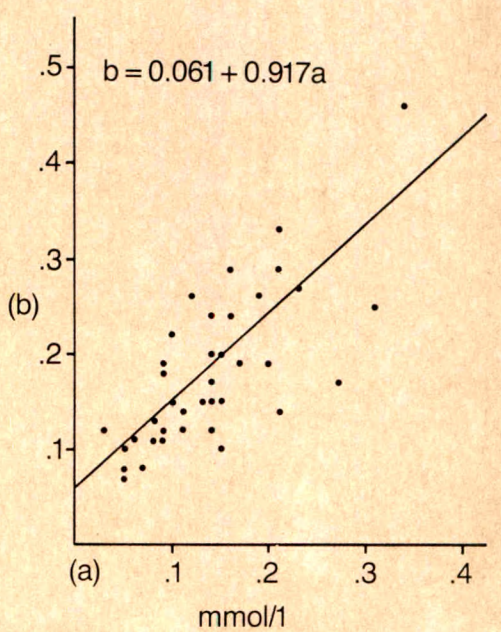

FIGURE 6. High-density lipoprotein $cholesterol_2$ levels (**a**) before treatment and (**b**) after treatment.

TABLE II Variation in Plasma High-Density Lipoproteins and HDL_2 Before and After Cardiac Rehabilitation in Relation to Cigarette Smoking Habits

	Wilcoxon Test	Correlation Coefficient	ANOVA	Ratio Test	% Change
HDL nonsmokers (n = 19)	X*	XXX†	XXX	XX‡	+39.87
HDL reduced/stopped (n = 15)	XXX	XXX	XXX	XXX	+58.27
HDL smokers (n = 6)	NS	NS	NS	NS	+6.13
HDL_2 nonsmokers	XX	XX	X	XXX	+23.38
HDL_2 reduced/stopped	XXX	XXX	XXX	XXX	+73.75
HDL_2 smokers	NS	NS	NS	NS	+8.64

* X = $p < 0.05$.
† XX = $p < 0.01$.
‡ XXX = $p < 0.001$.
ANOVA = analysis of variance; HDL = high-density lipoprotein; NS = not significant.

TABLE III Significance of Differences Between Regression Lines for High-Density Lipoprotein Levels Before and After Rehabilitation Course

	HDL	HDL_2
Nonsmokers versus smokers	$p < 0.01$	$p < 0.01$
Ex-/reduced smokers versus smokers	$p < 0.001$	$p < 0.001$
Nonsmokers versus ex-/reduced smokers	$p < 0.05$	$p < 0.05$

HDL = high-density lipoprotein.

a 33-meter pool and to play a couple of games of volleyball as well, which is very hard exercise. This amount has been achieved safely and within a few weeks of myocardial infarction or coronary artery surgery. Moreover, we have shown that this short, intensive course of exercise produces highly significant changes in plasma HDL, which may be prognostically favorable if maintained (Table III).

Continued cigarette smoking, however, virtually negates these changes. A recent study from Lund, Sweden, of HDL levels after smoking was stopped, performed by Stubbe et al,[4] showed a 29% increase in 2 weeks, but it was notable in our study that HDL changes were equally significant in the nonsmokers and in those who quit.

Acknowledgment: I would like to thank many members of the staff of my own hospital for their assistance and particularly Professor Barry Lewis and his staff at St. Thomas' Hospital for their help with this work.

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Influence of Diet on High-Density Lipoproteins

GÜNTER SCHLIERF, MD, LENORE ARAB, MD, and PETER OSTER, MD

Evidence of a relation between diet and high-density lipoprotein (HDL) levels in humans comes from numerous cross-sectional and experimental studies. Evaluation of data from cross-sectional nutrition and health surveys sometimes yields different results for men and women but usually demonstrates positive correlations of HDL cholesterol levels with total energy intake, alcohol consumption, dietary cholesterol and total and animal fat, and negative correlations of HDL with dietary carbohydrates (simple sugars) and, in some instances, plant fats. Short-term dietary manipulation produced confirmatory evidence of a causal relation between diet and HDL with regard to several of these factors; however, there are few long-term data.

The underlying mechanisms as well as the relation of HDL manipulation to cardiovascular health are still to be defined, particularly because the functions and fates of the HDL molecule may vary according to its composition and turnover, which are not reflected by the HDL cholesterol concentration. Furthermore, some relations between diet and HDL may only be the result of other metabolic consequences of dietary change, for instance, triglyceride metabolism and other lipoproteins.

Although there is consistent evidence that a high HDL cholesterol level is indicative of a low risk of coronary heart disease in industrialized populations, evidence is inconclusive that manipulation of HDL leads to an alteration of risk.

Because plasma lipoproteins are either directly or indirectly derived from the food we eat, it is not surprising that diet affects lipoprotein concentrations in a powerful way. Epidemiologic studies and controlled experiments support the theory that atherogenic lipoprotein patterns and concentrations in most cases have environmental origin and, thus, essentially are amenable to normalization. High-density lipoprotein (HDL) cholesterol levels differ from person to person, and the plasma concentration can be induced to increase or decrease by factors that we can manipulate. Diet is prominent among these factors. Although this brief report reviews some dietary effects on HDL, there is little unequivocal evidence on this topic. Different studies have given different answers owing to different methods and, possibly, different responsiveness of persons. Duration of experiments may also be a crucial factor, and adaptation to the situation may occur.

Most people in discussing or studying HDL actually discuss and study HDL cholesterol, which is but 1 constituent of HDL. It may not always reflect the actual concentration of these lipoproteins, which have a density >1.063, particularly when the ratio of HDL subclasses is altered or when dietary changes lead to compositional changes of HDL particles. Even when dietary effects on HDL have been established, such as the occurrence of a particular HDL on high-cholesterol diets as described by Mahley,[1] conclusions about the long-term health consequences of such changes remain tentative. With these precautions, the following brief report is given.

Cross-sectional studies: Data from cross-sectional studies can be found in our survey of 20- to 40-year-old Heidelberg men and women.[2] We established dietary habits and measured lipoproteins. Significant positive correlations with HDL cholesterol were found for dietary energy, probably mediated by energy expenditure, and for alcohol (Fig. 1). An inverse (negative) relation was noted for sugar intake (Fig. 2) and plant fat intake (Table I). In addition, other studies of similar design found positive correlations with total and animal fat as well as with dietary cholesterol.

Interpretation of such cross-sectional correlation data requires 2 considerations. The first is that correlations do not establish causality, and the second is that noncorrelations do not establish ineffectiveness of the respective dietary factor.

Complementary evidence comes from the study of populations with different dietary habits, for example,

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TABLE I Multiple Regression Analysis on High-Density Lipoprotein (HDL) Cholesterol, HDL/Total Cholesterol, and Low-Density Lipoprotein/HDL Cholesterol

Independent Variables*	HDL Cholesterol	HDL/Total Cholesterol	LDL/HDL Cholesterol
Energy intake	+	+	−
Disaccharides	−	−	+
Alcohol	+	+	−
Plant fat	−	NS	NS
Animal fat	NS	NS	+
Polysaccharides	NS	NS	NS

* Other independent variables were smoking, contraceptives, triglycerides and age.
LDL = low-density lipoprotein; NS = not significant; + = increase; − = decrease.

TABLE II Plasma Lipid and Lipoprotein Concentrations in Vegetarians (mg/dl, Mean ± Standard Deviation)

	Vegetarians (n = 7)	Nonvegetarians (n = 6)
Plasma cholesterol	140 ± 18	190 ± 22*
Plasma triglycerides	99 ± 17	102 ± 39
LDL cholesterol	87 ± 21	123 ± 28†
HDL cholesterol	40 ± 5	44 ± 7
LDL Apo B	57 ± 14	84 ± 20†
Plasma Apo A-I	99 ± 18	120 ± 21

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* $p < 0.01$
† $p < 0.05$
Apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE III Lipoprotein Triglycerides and Cholesterol with High- and Low-Carbohydrate Diets*

		Carbohydrate Diet	
		Low	High
Fraction		Mean ± SD	Mean ± SD
VLDL	TG	10.8 ± 10.7	41.4 ± 21.2†
	Chol	6.4 ± 5.9	5.7 ± 6.2†
LDL	TG	15.7 ± 10.3	23.8 ± 10.7†
	Chol	119.6 ± 15.7	90.2 ± 25.3†
HDL	TG	3.0 ± 3.8	11.4 ± 3.8†
	Chol	37.5 ± 9.3	26.5 ± 9.5†

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* Ten-day periods.
† $p < 0.05$; n = 12.
All values are in milligrams per deciliter.
Chol = cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; TG = triglycerides; VLDL = very low density lipoproteins.

TABLE IV Effect of Dietary Changes on Low-Density Lipoprotein Cholesterol

	Groups		
	Treated	Control	p Value
HDL cholesterol (mg/dl)	50	42	<0.01
Total cholesterol (mg/dl)	263	341	<0.001
LDL cholesterol (calculated)	187	258	<0.001
Triglycerides (mg/dl)	129	200	<0.01
Relative body weight	23	26	<0.01

Reproduced from Hjermann et al[7] with permission of the publisher.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

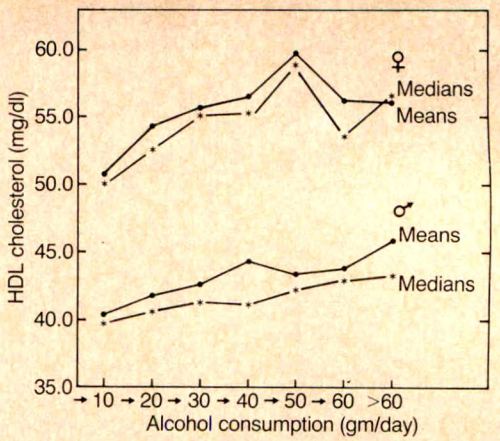

FIGURE 1. High-density lipoprotein (HDL) cholesterol and alcohol consumption (Heidelberg study).

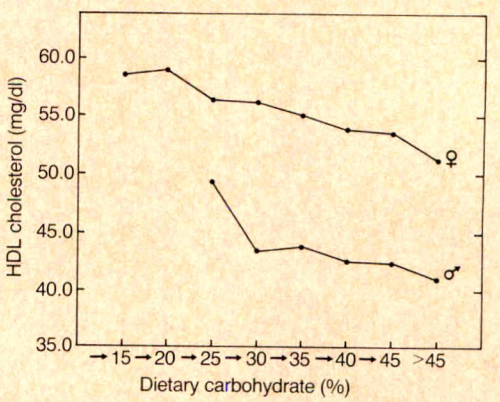

FIGURE 2. High-density lipoprotein (HDL) cholesterol and relative amount of dietary carbohydrate (Heidelberg study).

vegetarians.[3] The vegetarian diet is low in total and animal fat, cholesterol and sugar and is high in carbohydrates, fiber and plant fat. The lipoprotein patterns are characterized by substantially lower total and low-density lipoprotein (LDL) cholesterol concentrations, but also lower HDL cholesterol concentrations (Table II). Data on cardiovascular health in these people support the theory that HDL must be evaluated in relation to LDL and that low HDL may lose its role as a risk indicator if LDL is also low.

Controlled dietary experiments: Controlled dietary experiments are a more direct approach to the study of diet-HDL relations. Data from our metabolic ward[4] on the effect of a prudent diet in familial hypercholesterolemia and in endogenous hypertriglyceridemia show that a fat-modified, low-cholesterol diet given for 3 weeks, while appreciably affecting LDL and very low density lipoprotein (VLDL) levels, has no effect on HDL cholesterol concentrations. Others, using similar diets, even found an acute decrease in HDL cholesterol, with a lipid-lowering prudent diet.[5] Such an acute decrease in HDL cholesterol was shown in an experiment in which subjects were switched from a high-fat, low-carbohydrate diet to a low-fat, high-carbohydrate diet.[6] This marked decrease in HDL cholesterol was seen concomitant with changes in other lipoproteins (Table

III). Because such a considerable decrease in HDL cholesterol is not observed in populations on habitual high-carbohydrate diets, we speculate that concomitant with the reversal of carbohydrate-induced hypertriglyceridemia, HDL cholesterol would increase upon continuation of such diets for months or years.

Confirmatory evidence for this theory of a difference in short- and long-term dietary effects is supplied by data from the Oslo study.[7] In this long-term experiment on the effects of a prudent diet, along with the predicted changes in total cholesterol and LDL cholesterol, there was an increase in HDL cholesterol (Table IV).

An interesting hypothesis put forward by Knuiman and West[8] is that high HDL cholesterol is a negative risk factor or indicator in populations on high-fat diets because it reflects the ability to handle dietary fats. Low HDL found in many populations or groups on low-fat diets would lose its role as an indicator of risk because the challenge of fat loads is lacking. Thus, only on a high-fat diet, low HDL cholesterol indicates a high risk, and higher HDL cholesterol levels, lower risks.

I would like to have discussed experiments on the effect of meat versus fish protein, of different dietary fibers, of vitamin and mineral supplementation, of total fasting or of hyperalimentation, which have all been studied since HDL became "famous." Because space does not permit, I will summarize. Dietary factors do influence HDL. Acute effects probably differ from long-term effects. In most studies, a prudent diet, owing to its dominant influences on LDL, favorably affects LDL:HDL ratios. If LDL and HDL are low on a low-fat diet, this finding appears also to be consonant with a low cardiovascular risk. If HDL levels are low on a high-fat diet, do worry. Do not worry about HDL cholesterol on a low-fat diet. Much work remains to be done to answer the key question: whether manipulating HDL by any means leads to alteration of risk of coronary heart disease.

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Discussion—High-Density Lipoproteins: Epidemiology and Physiologic Influences

GÜNTER SCHLIERF, MD, Moderator

Dr. Kostner (Graz, Austria): It has been pointed out in almost every report presented that HDL is a composition of several classes or families. It has also been shown that by measuring HDL_2, one can possibly discriminate better than by measuring total HDL. My question to Tony Gotto or Barry Lewis, therefore, is, can we recommend any fraction within HDL that may discriminate better than total HDL?

Dr. Gotto (Houston, Texas): If it is possible in a particular clinical laboratory, I would prefer having a measurement of HDL_2. If that's not feasible, then I would take a total measurement of HDL cholesterol.

Dr. Lewis (London, England): Yes, I concur with that. The options, then, in doing so are to use a precipitation method or ultracentrifugation. The 2 correlate reasonably closely, although the results are not identical. We have found very satisfactory the use of a small air-driven ultracentrifuge made by Beckman that produces HDL_2 results within about 3 hours.

Dr. Schlierf: The specific part of the question was whether measurement of one of the apolipoproteins could replace the more cumbersome subfractionation of HDL. Would you say a word on this, Dr. Gotto?

Dr. Gotto: I am not sure I can answer that question at the moment. The measurement of apoproteins and apoprotein subfractions is coming into its own. At present, this is still experimental. Apo A-I will correlate more closely with HDL_2 than with HDL_3, but the difficulty in making the correlations with the apoprotein concentrations is that on a very low cholesterol diet the proportion of apoprotein in the lipoprotein family increases. This is true of all lipoprotein families, whether LDL or HDL. We do not know at the moment how to interpret these findings. What is the significance of the finding that the apo A-I increases out of proportion to the amounts of cholesterol? Questions have also been raised about whether apo B itself is a risk factor. Until we have epidemiologic information of the kind Dr. Kannel was discussing, I think that this still has to remain in the level of experimental work.

Dr. Schlierf: Thank you. The next question please.

Dr. Förster (Halle, German Democratic Republic): I would like to mention a point of view not discussed in these reports. For many years we have been trying to assess the influence of lipoproteins on prostacyclin biosynthesis. Many investigators believe that in atherogenesis the antiaggregatory effect of prostacyclin may be important, and we could show that HDL has an increasing effect on the prostacyclin synthesis activity, whereas LDL has a decreasing effect. These differences seem to be specific and are dependent on sex and also on age. There were differences in premenopausal and postmenopausal women. We believe this new point of view should be incorporated in the discussion of the pathogenesis of atherosclerosis.

Dr. Schlierf: Thank you for this interesting and timely contribution. Dr. Smith, your question please.

Dr. Smith (Aberdeen, Scotland): I was fascinated by Colonel Cowan's statistics on a 6-fold difference in coronary risk between the enlisted men and the Sandhurst officers. I wonder if you have any lipoprotein data on these 2 groups?

Dr. Cowan (London, England): Unfortunately not. In our organization we are always reluctant to bleed men in large numbers. Although obviously it would be a very interesting study, it has not yet been done.

Dr. Schlierf: The next question is from Dr. Kumerow.

Dr. Kumerow (Chicago, Illinois): Dr. Gotto demonstrated the hydrophobic and hydrophilic effects on the HDL molecules when exposed to egg yolk. If the egg white had been included, would it have changed the ratio of the hydrophobic to the hydrophilic apoprotein?

Dr. Gotto: A low-cholesterol diet would increase the total proportion of apoproteins in HDL. It would also relatively decrease HDL_2 more than it would HDL_3. I have not thought about this question specifically, but I would predict that it would cause a relatively greater decrease in apo A-I, the more hydrophobic of the apoproteins.

Dr. Schlierf: Thank you. The last question.

Dr. Banta (Australia): I would like to comment on the role of HDL in reverse cholesterol transport. Much has been said about how this happens. If it does happen, it must involve an esterification of cholesterol by LCAT, but then there are a number of problems. Firstly, patients with high concentrations of HDL do not esterify more cholesterol; if anything, their rate of cholesterol esterification is lower. Therefore, it is difficult to regard the role of HDL in protection as being that of reverse cholesterol transport. The second point is that if you make very simple arithmetic calculations on the amount of HDL being removed from the plasma, even if 100% of the HDL in human plasma were taken up by the liver, it accounts for the removal of only about 5% of the cholesterol ester formed. LDL, on the other hand, can account for about 80 to 90% of the cholesterol being removed from the plasma. We have to consider whether the correlations with HDL are reflections of other things. Possibly 1 thing we are currently not measuring in overnight fasted blood samples relates to the concept of the 24-hour integrated chylomicron membrane concentration. I do not know how we could measure it.

Influence of Bezafibrate, Fenofibrate, Nicotinic Acid and Etofibrate on Plasma High-Density Lipoprotein Levels

RODOLFO PAOLETTI, MD, GUIDO FRANCESCHINI, PhD, and
CESARE R. SIRTORI, MD, PhD

Increased levels of plasma high-density lipoprotein (HDL) cholesterol have been described after exposure to different dietary (such as ethanol) and environmental (such as chlorinated pesticides) factors as well as intense physical training. Several lipid-lowering drugs have also been shown to elevate HDL cholesterol. These findings are of particular interest, because adult levels of the putatively protective lipoprotein fraction appear not to be regulated by genetic factors.

Four hypolipidemic drugs are herein considered, all of which reportedly elevate HDL cholesterolemia. Two of them, bezafibrate and fenofibrate, belong to the class of "fibrate" derivatives; nicotinic acid (NA) and etofibrate (E) show some similarities, E being the chemical association between nicotinic acid and clofibrate. In most studies, bezafibrate (B), with a very short half-life (2.1 hours), has induced an HDL cholesterol elevation of about 20%, both in types II and IV hyperlipidemic patients; it is controversial whether HDL_2 rather than HDL_3 levels are elevated by B. Fenofibrate (F) shows prolonged plasma half-life in man (>21 hours) and markedly increases HDL cholesterol levels, particularly in type IV patients; data are less homogeneous in type IIA and IIB cohorts. It appears that F may increase apoprotein C-II levels in very low density lipoproteins, possibly an index of stimulated lipoprotein lipase activity. Both B and F may behave as "catabolic agents," stimulating the breakdown of triglyceride-rich lipoproteins and the transfer of surface components (free cholesterol) to HDL. A different case may be that of NA, which prevents the decrease of HDL cholesterol induced by carbohydrate-rich diets in volunteers. NA reduces the catabolism of HDL and markedly increases (300% or more) the HDL_2/HDL_3 ratio in both volunteers and type IV patients, but not in type IIB patients. Whether, in addition to a "sparing" action on HDL, NA may also increase HDL levels by stimulating lipoprotein lipase activity is being disrupted. Finally, E may increase HDL cholesterol by 10% or more while exerting significant hypocholesterolemic activity. This compound is of interest because it may stimulate the release of prostacyclin from the arterial wall; prostacyclin may be derived from HDL phospholipids, unusually rich in arachidonic acid. This observation may offer another clue to the understanding of the mode of arterial protection exerted by HDL.

The association between elevated high-density lipoprotein (HDL) cholesterol levels and reduced prevalence of ischemic events in the heart,[1] brain[2] and possibly other vascular areas[3] seems well established. However, aside from the epidemiologic implications of this finding, few if any data support the potential benefit of increasing HDL cholesterolemia. Indeed, dietary treatments for hyperlipidemia, particularly the use of diets rich in polyunsaturated fatty acids, seem to reduce rather than increase HDL cholesterol levels.[4] Currently, only ethanol, among dietary components, has been associated with increased HDL cholesterol levels.[5]

Despite an apparent inclination toward a prevalent role of genetic factors in regulating HDL cholesterolemia, still the role of "environmental" agents seems essential. In fact, no genetic link could be detected between the HDL cholesterolemia of parents and children,[6] indicating that adult levels of this presumably protective lipoprotein fraction are markedly regulated by other factors. Among these, hormones undoubtedly play a role,[7] as certainly also do ethanol consumption,[5] physical exercise[8] and environmental pollutants stimulating HDL production.[9] However, it is still controversial which of the 2 subfractions of HDL, that is, HDL_2 and HDL_3 (see other reports in this symposium), is specifically increased by each environmental, dietary and drug factor. This controversy stems in part from the uncertain definition of which of the 2 HDL subfractions exerts the "protective" role in atherogenesis.[10]

Because adult HDL cholesterol levels are a product of numerous external factors, a distinct possibility exists that drug treatment, if positively affecting HDL cholesterolemia, might also provide a useful therapeutic mode of prevention of arterial degenerative disease. In

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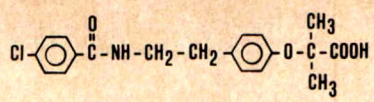
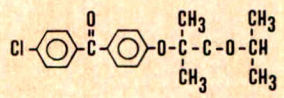
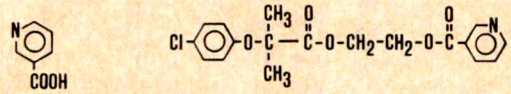


BEZAFIBRATE



PROCETOFEN



NICOTINIC ACID

ETOFIBRATE

IGURE 1. Structural formulas of bezafibrate, fenofibrate (procetofen), cotinic acid, and etofibrate.

his brief review, 4 different drugs, all reportedly ele-ating levels of HDL cholesterol, are examined in terms f both their general pharmacologic properties and their ode of eliciting elevated levels of this possibly pro-ective lipoprotein.

Pharmacologic Characterization of the Compounds

Two agents under evaluation belong to the general oup of aryloxyacids, the prototype of which is clofi-rate.[11] Nicotinic acid seems to share some of the roperties of the "fibrate" derivatives, such as the ac-vation of lipoprotein lipase,[12,13] but also shows prop-ties of its own, particularly reduced adipose tissue polysis.[14] Finally, etofibrate shares some of the prop-ties of both "fibrates" and nicotinic acid, being a olecular association of the 2 compounds (Fig. 1); ap-arently, etofibrate may display some of the beneficial properties of the components, but with a lower incidence of side effects, compared with nicotinic acid.

Bezafibrate: The general pharmacology of this agent is quite similar to that of clofibrate; that is, it induces particularly both a marked reduction in plasma cholesterol levels[15] and a significant liver weight gain[16] in rodents on hyperlipidemic regimens. Bezafibrate is 3 to 4 times more potent than clofibrate in standard tests of hyperlipidemia. The liver weight gain in rodents after bezafibrate results, as with clofibrate, from the proliferation of peroxisomes.[17]

Kinetic studies with bezafibrate in man, however, show considerable differences from clofibrate. The apparent half-life of bezafibrate in serum is, in fact, only about 2.1 hours,[18] compared with 10 to 30 hours for chlorphenoxyisobutyric acid, the active metabolite of clofibrate. The relatively rapid absorption and elimination, with a very high plasma clearance (around 100 ml/min), indicate favorable pharmacokinetic properties. The short half-life and efficient clearance (half renal and half metabolic) make cumulation highly unlikely.

Fenofibrate: Fenofibrate displays very effective cholesterol- and triglyceride-lowering activities in animal models, being at least 10 times more potent than clofibrate.[19] Similarly to bezafibrate, fenofibrate induces peroxisome proliferation and liver weight gain in rodents.[17]

Differently from bezafibrate, fenofibrate has a prolonged plasma half-life in man. The drug is only moderately well absorbed in the unchanged form (about 30%), being eliminated as free acid. Terminal plasma half-life is in excess of 21 hours,[20] apparently unchanged after long-term treatment and not influenced by concomitant intake of anion exchange resins.[21] Differently from bezafibrate, fenofibrate may therefore not require repeated administration during the day.

Nicotinic acid: The mode of the lipid-lowering action of nicotinic acid has been the subject of many reports, mainly indicating the powerful antilipolytic activity of the agent,[14] which is not reviewed herein.

The metabolic fate of nicotinic acid is complex, leading to conjugative products (methyl or glycine

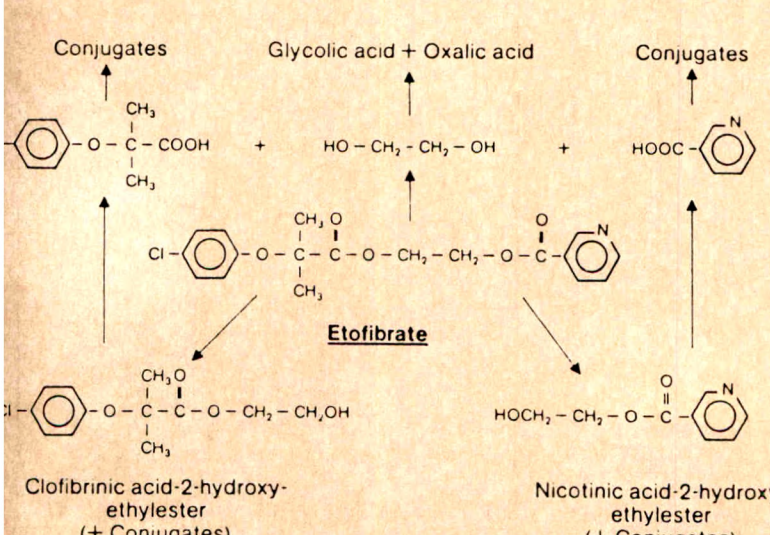


FIGURE 2. Metabolic breakdown pattern and major catabolic products of etofibrate in man.

conjugates) and to other oxidated metabolites.[22] In general, the compound undergoes extensive first-pass handling, with the formation of nicotinuric acid taking place within the first 2 hours of the dose, followed by a slower metabolic pathway (essentially with methylated metabolites) proceeding for more than 12 hours.[23] With larger doses (exceeding several grams per day), metabolism is considerably altered, with more than 80% of the administered drug appearing in an unchanged form in the urine.

The major side effect of nicotinic acid administration, dilation of superficial vessels, with a characteristic "flush," appears in the first 10 to 20 minutes after administration and is closely correlated with the increase in nicotinic acid levels in plasma.[24] With repeated doses a gradual tolerance develops, so that flushing tends to become less severe, although it usually continues to some degree after each dose. Of the many nicotinic acid derivatives in clinical use, nicotinyl alcohol, D-glucytol hexanicotinate (sorbinicate)[25] and pentaerythritol tetranicotinate (niceritrol)[26] are the most widely used, being effective at lower doses and with less severe side effects. More recently, the pyridine N-oxide analog of nicotinic acid (acipimox) has shown an impressive pharmacologic profile[27] and a valid lipid-lowering activity in man.[28]

Etofibrate: Etofibrate is the condensation product of clofibrate and nicotinic acid, giving rise to a variety of metabolic derivatives (Fig. 2). The fate of the 2 major metabolites, clofibrate and nicotinic acid, is similar to that of the 2 parent drugs. Etofibrate apparently has a reduced acute toxicity compared with clofibrate and clofibric acid, and is well tolerated on prolonged administration. In rodents, etofibrate shows more marked cholesterol-lowering activity than clofibrate.[29] This agent produces a lower incidence of side effects in man compared with nicotinic acid.[30]

Potential Mechanisms of the HDL Increase Induced by Drugs

Plasma HDL levels, as pointed out, are influenced by a variety of factors. HDLs are secreted from the liver and intestine. The quantitative analysis as well as the chemical composition of particles secreted by the 2 tissues are the object of other presentations in this symposium. Catabolism of HDL occurs mainly in the liver and may be influenced by dietary fat and carbohydrate intake.

Two general mechanisms seem to be involved in determining the final levels of HDL and particularly of HDL cholesterolemia: (1) changes in HDL metabolism after alterations in the synthetic or catabolic rates of HDL and their polypeptides, or both, and (2) alterations in lipoprotein interconversion through control of the key enzymes involved in the process.

High-carbohydrate diets reduce HDL cholesterol levels in association with an increased turnover of HDL particles.[31] Moreover, lipid-lowering, fat-controlled diets may reduce HDL cholesterol and apoprotein A-I levels, possibly by decreasing the intestinal synthesis of apo A-I–containing lipoproteins.[32] In contrast, diets high in cholesterol and saturated fat increase both HDL cholesterol and plasma apo A-I levels,[33] also inducing the formation of apo E–containing lipoprotein particles in the HDL density range.[34]

An increase in HDL levels may also occur after treatment with agents that increase liver protein synthesis, such as enzyme inducers. Such findings have been reported with antiepileptic agents in man;[35] exposure of experimental animals or man to TCDD or to chlorinated insecticides also increases HDL cholesterol levels.[9,36]

A possible major mode of action of drugs affecting HDL cholesterol levels may be related to changes in the interconversion of lipoprotein particles in the blood. During catabolism of very low density lipoproteins (VLDL), surface material, such as apolipoproteins and cholesterol, is transferred to the HDL pool.[37] An increase in VLDL turnover is produced by a variety of factors stimulating the activity of the lipoprotein lipase (LPL) enzyme. Among environmental factors, such a mechanism has been postulated for physical exercise and for alcohol consumption. Increased HDL cholesterolemia and apo A-I levels are detected in physically well-trained men and may be induced by appropriate exercise programs.[8] An increase of LPL activity may be detected in both adipose tissue and skeletal muscle during training.[38] Chronic consumption of ethanol has also been associated with increased LPL activity and elevated HDL cholesterol levels.[39]

Different mechanisms have been postulated for the modulation of HDL levels by sex hormones. Women have higher levels of total HDL and HDL_2 but lower HDL_3 concentrations than men.[7] The administration of estrogens to persons of either sex increases HDL levels, which conversely are reduced by androgenic and progestational hormones.[40] Changes in HDL cholesterol levels during the use of contraceptive preparations are generally related to the estrogenic or antiestrogenic activity of the progestogen in the pill.[41] Interesting effects may be displayed by sex hormones on hepatic lipase, an enzyme involved in the catabolism of HDL particles. Estrogens, in fact, suppress hepatic lipase activity and induce an increase in HDL; androgens stimulate this enzyme activity, decreasing HDL levels.[42]

An increase in HDL concentrations should be a definite aim in the treatment of patients with hyperlipidemia. The most commonly used hypolipidemic agents generally produce such an effect. A direct influence on HDL metabolism has also been suggested for cholestyramine, which may increase the HDL_2/HDL_3 ratio and apo A-I levels by increasing the synthetic rate of apo A-I.[43] The effect of the "fibrate" derivatives seems to be related to increased LPL activity, best noted in subjects with depressed VLDL catabolism. Finally, nicotinic acid and derivatives may act by the same mechanism as the "fibrates" and may also inhibit the catabolism of HDL.

Bezafibrate: Bezafibrate has shown somewhat better plasma cholesterol- and triglyceride-lowering activity compared with the reference compound.[44] In patients with hypertriglyceridemia, bezafibrate decreases plasma total and VLDL-associated triglycerides by about

45%.[45] Several investigators have reported increases in HDL cholesterol levels of about 20%.[45,46] An increase in cholesterol and apo A-I in the HDL_2 subfraction has been reported[47] (Fig. 3); however, recent findings indicative of a reduced ratio between plasma apo A-I and A-II levels during bezafibrate treatment suggest a probable increase in HDL_3.[45,48] The significance of these discrepancies is unclear. Bezafibrate improves plasma postheparin LPL activity and intravenous fat tolerance;[45] this possible mechanism of the hypotriglyceridemic effect of bezafibrate is consistent with an increase in the HDL_2 subfraction as a product of the catabolism of triglyceride-rich lipoproteins.[37]

In patients with hypercholesterolemia, bezafibrate increases HDL-associated cholesterol, apo A-I and apo A-II; these HDL components are still elevated 6 weeks after discontinuation of therapy,[49] thus indicating a prolonged effect of the agent. Increased HDL cholesterol levels have also been reported in hyperlipidemic, non–insulin-dependent patients with diabetes; in the same patients, lecithin cholesterol acyl transferase activity does not change, suggesting a lack of effect of bezafibrate on the interconversion of HDL subspecies.[48]

Increased levels of HDL cholesterol after bezafibrate treatment have not been noted consistently by all investigators.[50] However, in all patients with hyperlipoproteinemia treated with the compound, improvements in the HDL/LDL and the apo A-I/apo bezafibrate ratios have always been observed. These findings indicate that bezafibrate treatment may effectively reduce lipoprotein-linked atherogenicity.

Fenofibrate: Fenofibrate, a clofibrate derivative, shows a powerful hypolipidemic activity at relatively small daily doses (300 to 400 mg). It markedly depresses total plasma cholesterol and triglyceride levels in both patients with type II and those with type IV hyperlipidemia.[51] A recent comparative study with cholestyramine in type II patients indicates that fenofibrate is slightly more effective than the anion exchange resin.[52] In all studies, fenofibrate treatment has led to a more favorable HDL/LDL ratio, mediated through a reduction in the atherogenic components and in most cases by increase in HDL levels. In some studies, however, a reduction in HDL cholesterol was reported in patients with type IIA disease.[53]

After the start of fenofibrate treatment, a rapid increase in plasma apo A-I levels may be detected (particularly in patients with type IIB disease).[51] The absence of a concomitant increase in HDL cholesterol suggests a quantitatively different effect of fenofibrate on the 2 components of HDL, that is, cholesterol and apoproteins. However, HDL cholesterol increase in type IV patients is constant and reproducible in all studies (Fig. 4).

The mechanism of the hypolipidemic effect of fenofibrate is still incompletely clarified. An increase in the apo C-II content and the apo C-II/C-III-1 ratio in VLDL has been described by our group (Fig. 5). This finding is consistent with the observed increase in LPL activity after fenofibrate treatment.[54] Therefore, fenofibrate appears to belong to a group of drugs that exert mainly a catabolic effect on triglyceride-rich lipoproteins. This effect may result in increased HDL cholesterol levels, particularly in patients with hypertriglyceridemia.

Nicotinic acid: Treatment with large doses of nicotinic acid is generally associated with a marked reduction in both plasma cholesterol and triglyceride levels of about 15 to 20% and 45 to 50%, respectively. More recently, increases in HDL cholesterol have been reported by several investigators[55] and studies have been carried out in both normolipidemic volunteers and pa-

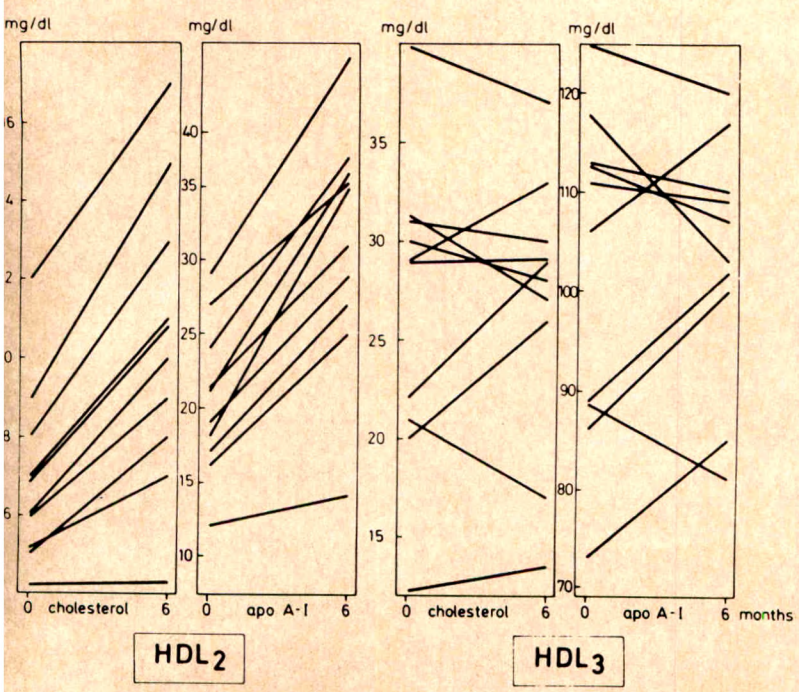


FIGURE 3. Increased concentration of cholesterol and apoprotein A-I in the HDL_2 subfraction after long-term treatment with bezafibrate. HDL_3 cholesterol and A-I levels are not affected.[47] HDL = high-density lipoprotein.

tients with hyperlipidemia to examine in detail the plasma lipoprotein changes as well as the mechanism of the HDL increasing effect.

In normolipidemic volunteers, Blum et al[31] indicated a counteracting effect of nicotinic acid on the HDL-decreasing activity of a high-carbohydrate diet. These investigators could clearly demonstrate that HDL catabolism was delayed by nicotinic acid administration and that the HDL_2/HDL_3 ratio in plasma, as determined by analytic ultracentrifugation, was elevated at least 300% after drug intake.

In healthy volunteers on a free diet, Shepherd et al[56] could confirm the HDL-elevating properties of nicotinic acid (3 g/day). The drug decreased plasma cholesterol 15% and triglycerides 27%; plasma HDL cholesterol was increased 23%, with a 345% increase in the plasma HDL_2/HDL_3 ratio (Fig. 6). This resulted from an absolute increment (+646%) in circulating HDL_2 and decrement (47%) in HDL_3 levels.

These investigators,[56] in types II and IV hyperlipidemic patients, could show somewhat divergent effects of nicotinic acid.[57] In the entire group of type II patients, only a reduction in plasma total triglycerides and VLDL cholesterol could be noted; no change was detected in total, LDL and HDL cholesterol levels. However, when

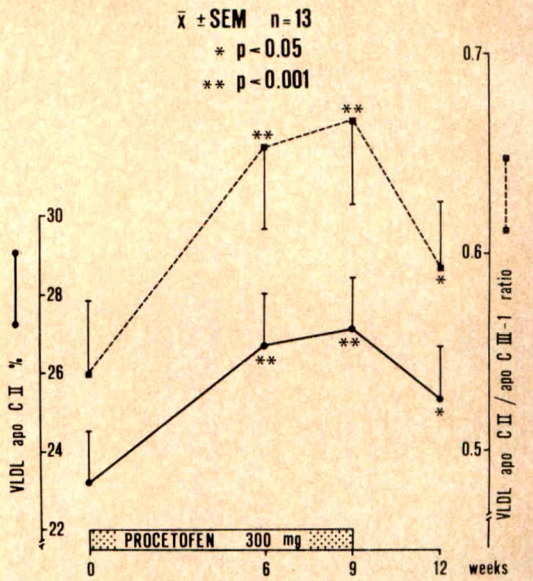


FIGURE 5. Progressive increase in the apoprotein C-II content and the apo C-II/C-III-1 ratio in very low density lipoprotein (VLDL) during fenofibrate (procetofen) treatment in patients with type IV hyperlipoprotenemia (same cohort as in Figure 4). Both apoprotein changes are reversible after the end of treatment. SEM = standard error of the mean.

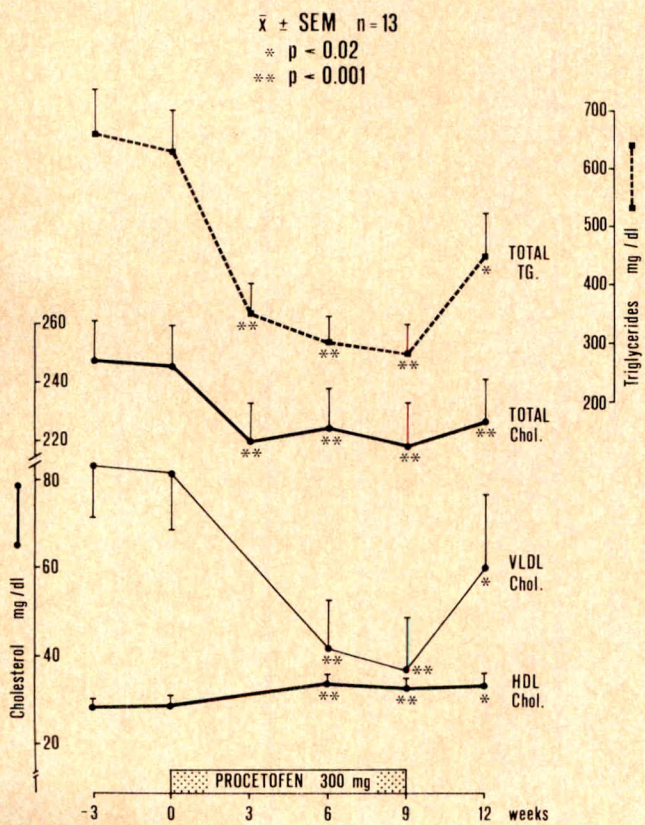


FIGURE 4. Plasma lipid and lipoprotein changes in patients with type IV hyperlipoproteinemia during and after the administration of fenofibrate (procetofen). An 11% increase in high-density lipoprotein (HDL) cholesterol may be noted, maintained after the end of treatment. Chol = cholesterol; TG = triglycerides; SEM = standard error of the mean; VLDL = very low density lipoprotein.

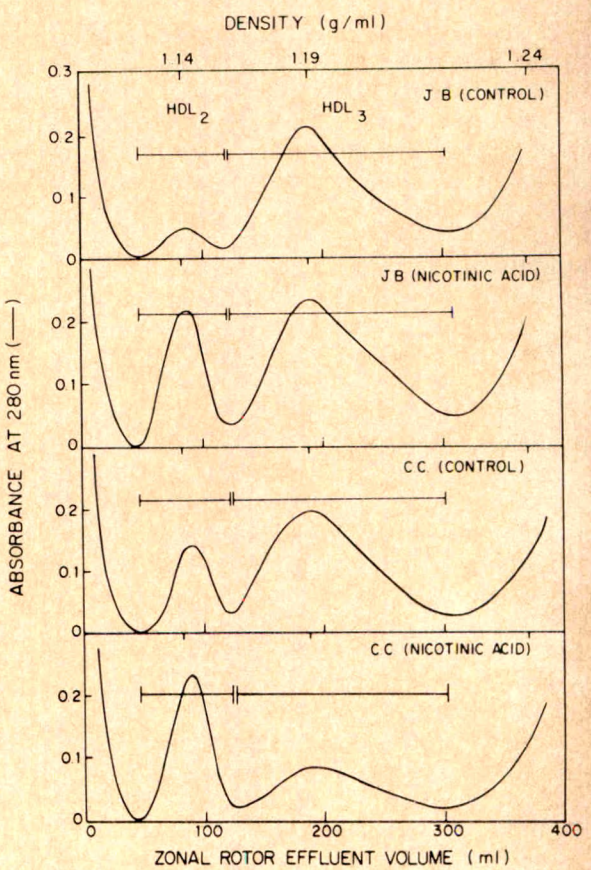


FIGURE 6. Separation of the high-density lipoprotein (HDL) subfractions by zonal ultracentrifuge before and after administration of nicotinic acid to normolipidemic volunteers. A dramatic increase in HDL_2 and a concomitant reduction in HDL_3 (particularly in subject CC) are noticeable.[56]

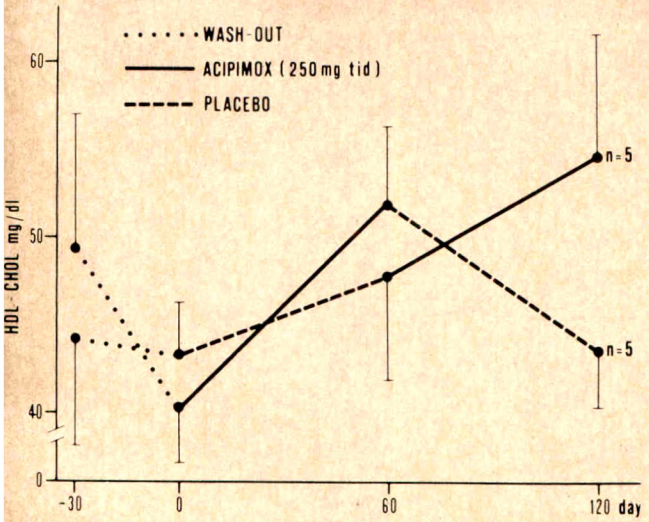


FIGURE 7. Changes in plasma high-density lipoprotein cholesterol HDL-CHOL levels in patients with type IIA hyperlipoproteinemia during a crossover trial of acipimox, a nicotinic acid analog, versus placebo. HDL cholesterol levels are about 20% higher during active drug treatment, the increase being reversible after the switch to placebo.[28] Tid = 3 times a day.

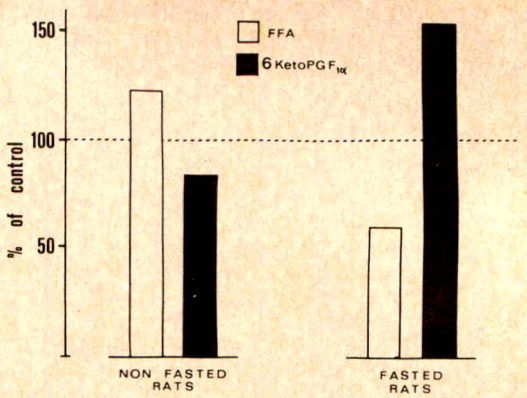


FIGURE 8. Free fatty acid (FFA) release from adipocytes and PGI_2 formation from adipose tissue arteries in rats treated with etofibrate (200 mg/kg). In fasted animals in which lipolysis is stimulated, an enhanced PGI_2 release together with FFA levels may be detected.[61]

only type IIA patients are considered, an increase in HDL cholesterol may be established (+37%) together with a striking increase (+510%) in the HDL_2/HDL_3 ratio. Patients with type IIB hyperlipoproteinemia were essentially insensitive to the lipid-lowering effect of the drug, and indeed, their HDL_3 levels increased 20%. Plasma lipid and lipoprotein changes in type IV patients were similar to those previously reported in normolipidemic subjects.[56]

Our findings with the nicotinic acid analog acipimox in hyperlipidemic patients are somewhat similar and somewhat at variance with those of Packard et al.[57] We failed to note any change in HDL cholesterol levels in type IV patients, whereas we did detect a significant increase in HDL cholesterolemia in type IIA patients (Fig. 7).[28] In this study, the reversibility of the HDL cholesterol increase (+20%) after the switch to placebo was clearly evident.

The mechanism whereby nicotinic acid increases HDL cholesterolemia may be linked to a reduced fractional catabolic rate of apoprotein A-I.[31] However, an increased HDL formation can be consequent also to stimulated VLDL lipolysis.[13] The inconstant effect on HDL cholesterol levels in the different hyperlipoproteinemia phenotypes is far from clear. It may generally be inferred that an increased formation of HDL_2 particles from HDL_3 is a frequent consequence of nicotinic acid treatment, thus possibly influencing plasma levels of the putative protective subfraction of HDL.

Etofibrate: This compound, despite extensive clinical experience, has not been the object of detailed investigations, particularly pertaining to the HDL lipid levels. In humans, as shown by Kaffarnik et al,[30] both plasma cholesterol and triglyceride levels are significantly reduced and the effect on HDL cholesterol, although consistent, is relatively small (around +10%). Similar findings, that is, an 18% reduction in total cholesterol with an 8% increase of HDL cholesterol, were recorded by Gustafsson[58] in patients with stable hypercholesterolemia; this author noted that plasma cholesterol had been decreased only 6% by previous clofibrate administration in the same cohort.

Aside from its lipid-decreasing activity, etofibrate is of interest because it shares with nicotinic acid the capacity to release prostaglandins from tissues and particularly from the arterial walls.[59] Our research group has placed particular effort into studies on the release of prostacyclin (PGI_2) from the arterial walls after the administration of nicotinic acid or etofibrate. PGI_2, an unstable metabolite of arachidonic acid, exerts powerful platelet antiaggregant and arterial vasodilator effects.[60] The release of PGI_2 from the endothelium after etofibrate administration is more prolonged than that exerted by nicotinic acid, owing possibly to the more stable plasma levels of nicotinic acid after the administration of etofibrate.[61] As shown in Figure 8, PGI_2 release from the arterial wall is particularly enhanced in fasted conditions in which adipose tissue lipolysis is stimulated and etofibrate is also capable of reducing free fatty acid levels.[61]

The potential capacity of drugs affecting HDL levels to stimulate PGI_2 release is a subject for future experimental and clinical studies. The 2 findings, elevated HDL levels and enhanced PGI_2 release, may be closely related because in mammalian species HDL are loaded with phospholipids rich in arachidonic acid.[62]

In conclusion, the increase in HDL cholesterol levels is a consequence of treatment with several pharmacologically active compounds. Although the mechanisms underlying this effect are not totally clarified, in most cases an activation of VLDL lipolysis, with consequent transfer of surface components to HDL, appears to be operative. Interestingly, PGI_2 release from the arterial wall may be stimulated by nicotinic acid derivatives as well as possibly by other hypolipidemic agents. Whether this vascular effect may partly explain the protective activity of HDL against the progression of atherosclerotic lesions remains to be established.

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Influence of Clofibrate, Bile-Sequestering Agents and Probucol on High-Density Lipoprotein Levels

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The management of lipid disorders has been greatly improved by advances in our understanding of lipoprotein metabolism. New developments in the isolation and quantitation of the lipoprotein apoproteins have shed light on their essential role in normal and abnormal lipid transport and have helped clarify the mode of action of lipid-lowering drugs. Excess lipid levels can occur because of overproduction, faulty degradation or defective removal of 1 or more lipoproteins.

Clofibrate appears to decrease levels of very low density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) by enhancing their intravascular degradation. Although it often slightly decreases low-density lipoprotein (LDL) levels, it may markedly increase LDL levels in patients with initially high VLDL levels. Its effects on high-density lipoproteins (HDL) are small, often increasing HDL slightly. Bile acid sequestrants act by enhancing the rate of removal of LDL. Their effects on VLDL and IDL are slight. In some subjects there is a moderate increase in both VLDL and IDL levels. HDL concentrations are increased minimally. Probucol's mechanism of action is still unclear, but it appears to enhance LDL removal. Its effects on VLDL and IDL are minimal. Of concern is the repeated observation that probucol reduces HDL concentrations by decreasing HDL synthesis. The resultant reduction in HDL concentrations often rivals its effect in decreasing LDL levels. Knowledge of the selective effect of lipid-lowering drugs on specific lipoprotein fractions is essential for their proper therapeutic selection.

The effects of clofibrate, bile acid–sequestering agents and probucol on high-density lipoproteins (HDL) will be discussed, followed by a description of gemfibrozil. I want to expand on a comment made by Dr. Lewis in this symposium and an additional question raised by Dr. Banta's comments. Although we are focusing on drugs and their effects on HDL, these drugs have pleomorphic effects on the lipoprotein family, and they must be considered simultaneously. Over the last 25 years many of us have been trying to provide conclusive evidence that a significant decrease in low-density lipoprotein (LDL) cholesterol will either retard the progression of atherosclerosis or induce its regression.[1–4] It is hoped that this question will be answered with the publication of the MRFIT studies and of the Lipid Research Clinics (LRC) program in 1984.

In addition to primary prevention of atherosclerosis with drugs in which LDL levels are decreased, many drugs are being evaluated, although not yet prospectively, in double-blind studies that will decrease triglyceride levels. Moreover, we should keep in mind an observation of low HDL cholesterol as a sole dyslipoproteinemia in subjects with premature coronary heart disease initially made by Nikkila[5] more than 20 years ago and recently brought home to us in our observation of familial hypoalphalipoproteinemia in children and their families with severe premature ischemic stroke:[6] that those persons with low HDL levels and otherwise normal lipids and lipoproteins are at high risk. There is a large population of persons with premature atherosclerosis who have normal total cholesterol, normal LDL and, usually, normal very low density lipoprotein (VLDL) levels and have as their characteristically abnormal lipoprotein low HDL of normal composition.[6] These families are riddled with premature heart disease and stroke. Some of the drugs we are discussing in this symposium have predominant effects on HDL and may be very useful in these persons.

Table I is a summary of the broad aspects of the various drugs we will discuss in this report, namely, clofibrate, the bile acid sequestrants, probucol and gemfibrozil. A few points of special interest will be discussed here.

First, there may often be a relative dissociation be-

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tween the effects of drugs on HDL and the effects of drugs on VLDL. Clofibrate, for example, has its predominant effect and use in decreasing VLDL and intermediate-density lipoproteins (IDL) (Table II).[7] It either decreases LDL modestly or, in persons with moderate-to-severe elevations of triglyceride, often elevates LDL or LDL apolipoprotein B, or both, an effect that may not be altogether desirable. Moreover, clofibrate has a relatively trivial effect, a plus-minus effect, on increasing HDL as compared with nicotinic acid, for example.

The bile acid sequestrants have, as their predominant effect, the effect being examined in the LRC trial and other trials—the lowering of LDL (Table III).[7,8] If anything, they modestly increase HDL levels in children and perhaps in young adults. In adults, bile acid sequestrants have a moderate effect—in most cases a very modest effect—and in patients with hypercholesterolemia, no effect on HDL levels.

Probucol, a recently released drug that significantly decreases LDL and has no effect on VLDL (Table IV), sharply reduces HDL,[7–9] so that the percentage reduction in HDL is greater than the percentage reduction in LDL, an effect that is puzzling and may be worrisome as well.

Gemfibrozil, a potent VLDL-lowering agent, perhaps similar in effect to nicotinic acid, has, like nicotinic acid, a very potent effect on increasing HDL. In our experience, gemfibrozil is also extremely effective in increasing HDL in persons whose sole lipoprotein abnormality is a low HDL level (Glueck et al, preliminary communication). Very much like clofibrate, and depending on the triglyceride level, gemfibrozil may either depress or slightly elevate LDL.

To comment briefly on the proposed mechanisms of action,[7] clofibrate appears to enhance the intravascular degradation of VLDL and LDL. The overall outcome of that effect is reflected in its depression of VLDL and IDL, which makes it so useful in familial type III disease. Unfortunately, perhaps as an outcome of this catabolic cascade, LDL levels and apo B in LDL are augmented particularly when the initial VLDL is elevated, and often there is an increase in biliary cholesterol, which leads to one of the major side effects of clofibrate, the effect on the gall bladder, and also to an increased amount of fecal neutral sterols that may essentially be related to the apparent increase of carcinoma reported in the World Health Study on clofibrate. Clofibrate, as already mentioned, has a plus-minus effect on HDL. As the VLDL, which was initially elevated, is reduced with clofibrate, there is often a modest, but certainly not dramatic, increase in HDL.

The proposed mechanism of action of the bile acid sequestrants is better understood: They enhance the removal of LDL.[7,8] It was recently shown that the administration of bile acid sequestrants in both normal persons and those with hypercholesterolemia leads to an induction of the apo B LDL-specific receptors, with enhanced catabolism of LDL. Hence, because such drugs have their predominant effect on LDL, it is not surprising that their effect on HDL is absent or minimal. Several years ago, Dr. Reginald Tsang and I made

TABLE I Effect of Lipid-Lowering Drugs on Lipoproteins

	Chylomicrons	VLDL	IDL	LDL	HDL
Nicotinic acid	+/—	↓↓↓	↓	↓↓	+/—
Clofibrate	---	↓	↓↓	+/—	+/—
Bile acid sequestrants	---	+/—	---	↓↓↓	---
Probucol	---	---	---	↓	↓
Gemfibrozil	+/—	↓↓↓	↓	↓	↑↑

HDL = high-density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins; ↑ = increase; ↓ = decrease.

TABLE II Clofibrate Profile

Proposed Mechanism of Action	Enhanced Intravascular Degradation of VLDL and IDL
Effects on lipoproteins	VLDL ↓ IDL ↓↓ LDL +/— often up when initial VLDL elevated HDL +/— often up when initial VLDL elevated

HDL = high-density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins; ↓ = decrease.

TABLE III Bile Acid Sequestrants (Cholestyramine, Colestipol) Profile

Proposed Mechanism of Action	Enhanced LDL Removal
Effects on lipoproteins	VLDL +/— IDL --- LDL ↓↓↓ HDL ---

HDL = high-density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins; ↓ = decrease.

TABLE IV Probucol Profile

Proposed Mechanism of Action	Enhanced LDL Removal; Decreased HDL Synthesis
Effects on lipoproteins	VLDL --- IDL --- LDL ↓ HDL ↓

HDL = high-density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins; ↓ = decrease.

TABLE V Nicotinic Acid Profile

Proposed Mechanism of Action	Decreased VLDL Synthesis
Effects on lipoproteins	VLDL ↓↓↓ IDL ↓ LDL ↓↓ HDL +/—

HDL = high density lipoproteins; IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins; ↓ = decrease.

an observation that has held up in several studies, although we cannot yet explain it, and it is that in children with heterozygous familial hypercholesterolemia, the bile acid sequestrants are often associated with a highly significant increase in HDL cholesterol, an increase that is continued throughout the dynamic change of HDL during adolescence. This is an area that perhaps deserves more evaluation.[10]

We know that if we enhance LDL removal, cholestyramine is a very effective agent in decreasing LDL. In the liver's attempt to respond to the bile acid feedback system, we often see an increase in VLDL and occasionally in IDL.

It is fair to say that probucol's proposed mechanism of action is still entirely speculative. I have offered some options here of enhanced LDL removal, which seems logical. I believe the studies by Nestel and Billington[11] show that initially this interesting drug decreases HDL synthesis. Probucol also probably decreases the synthesis of apo A-I. With probucol, what we see is an effect on 2 lipoprotein classes that may be independent. Certainly it substantially decreases LDL, although not nearly as much as cholestyramine or cholesterol resin, but probucol is easier to take, so the aggregate effect may be the same. At the same time, there is a proportionate, or perhaps a disproportionate, reduction in HDL cholesterol and apo A-I which, at least to extrapolate from the epidemiologic data, would not appear to be optimal in a pharmacologic agent.[7,8] I shall have further comments on this subject subsequently.

In summary, clofibrate has a modest to trivial effect on HDL, perhaps increasing it. Bile acid sequestrants have no real effect on HDL in adults; they produce a modest increase in HDL in children. Probucol produces a consistent 15 to 20% reduction in total HDL cholesterol and apo A-I.[9] Table V is a profile of nicotinic acid, which, among its other proposed mechanisms of action, probably decreases VLDL synthesis.

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Influence of Gemfibrozil on High-Density Lipoproteins

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In animal studies, gemfibrozil markedly elevates high-density lipoprotein (HDL) cholesterol levels. In humans with primary hyperlipoproteinemia and lipoprotein phenotypes IIA, IIB and IV, gemfibrozil, 1,200 mg/day, was associated with a 25%, 20% and 17% increase in HDL cholesterol, respectively. Gemfibrozil also substantially increased the ratio of HDL to total cholesterol, reflecting both an increase in HDL cholesterol and a decrease in very low density lipoprotein cholesterol and low-density lipoprotein cholesterol. Compared with a placebo in subjects with types IIA, IIB and IV lipoprotein phenotypes, therapy with gemfibrozil led to an increase of 33%, 34% and 23%, respectively, in the ratio of HDL cholesterol to total cholesterol. With gemfibrozil therapy, about 80% of subjects with hypertriglyceridemia had a reduction in triglycerides of 35% or a return to normal levels; 50% of subjects with hypercholesterolemia had a cholesterol reduction of 20% or a return to normal levels.

Gemfibrozil is a newly released drug that shows considerable promise. It is very intriguing for many reasons, particularly in the interaction of high-density lipoprotein (HDL) and very low density lipoprotein (VLDL) metabolism. Gemfibrozil is a chemical homolog of clofibrate and bezafibrate (Fig. 1). It is rapidly absorbed, plasma levels reaching a peak at about 1 or 2 hours after an oral dose, and tissue concentrations in animal models also peak rather briskly. I will summarize the animal studies on gemfibrozil available so far without going into the proposed or speculated mechanisms of each effect (Table I).

Gemfibrozil increases plasma HDL cholesterol in either the normal or the cholesterol-fed rat[1] and simultaneously produces a notable decrease in hepatic cholesterol[1,2] in the same rat model, accompanied by an increase in rat fecal sterol excretion. In normal female rats and in monkeys, gemfibrozil reduces plasma triglyceride levels, and in normal monkeys it produces a sustained reduction in these levels.[3] In normal rats, this drug is associated with a marked increase in lipoprotein lipase activity.

Table II presents a comparison of the results of 1,200 mg/day of gemfibrozil versus a placebo in a large multicenter study that will be described in more detail by other participants in this symposium.[4,5] There was a rather consistent percent change in triglyceride levels (Table III), a decrement of 40 to 45% by phenotype, and a rather substantive increase in HDL in each of these 3 groups. Although not shown here, preliminary data from our laboratory (Glueck and co-workers, preliminary communication) show a substantive increase of 20 to 25% in HDL in patients who have primary hypoalphalipoproteinemia without other recognized phenotypic lipoprotein abnormalities. As expected from the data in Table II, gemfibrozil compared with placebo increases the ratio of HDL to total cholesterol by as much as 20 to 30%.

I reiterate Dr. Barry Lewis' caveat that it has taken us almost 25 years to determine whether a reduction of low-density lipoproteins (LDL) will reduce atherosclerosis. It is hoped that it will not take another 20 years to determine whether increasing HDL will also be effective.

In terms of the mechanism of action of this interesting drug, we have limited but useful data. Nikkila et al,[6] in a study of a group of 20 subjects with hypertriglyceridemia, found a highly significant reduction of 45 ± 4% in triglyceride levels and a trivial reduction (11%) in total cholesterol, reflecting a decrease in VLDL but an increase in HDL. Postheparin lipolytic activity increased in 19 of 20 subjects, but this average increment of 18% was only marginally significant, and the decrease in triglyceride levels in these subjects in no way correlated with the increase in lipoprotein lipase. Interestingly and somewhat confusingly, given what we now know about the inverse relation of hepatic lipase to HDL, hepatic lipase levels increased in these subjects by 21%, but the decrease in triglyceride levels did not correlate with the increase in hepatic lipase. Nikkila et al[6] speculated that the substantial increase in VLDL catabolism was most likely not the major effect of

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TABLE I Summary of Effects of Gemfibrozil in Animal Studies

Study	Effect
Plasma HDL in normal or cholesterol-fed rat	Marked elevation
Hepatic cholesterol in cholesterol-fed rat	Marked decrease
Rat fecal sterol excretion	Marked increase
Plasma triglycerides in normal female rat	Reduction
Plasma triglycerides in normal monkeys	Sustained decrease
Lipoprotein lipase activity in normal rat	Marked increase

HDL = high-density lipoprotein.

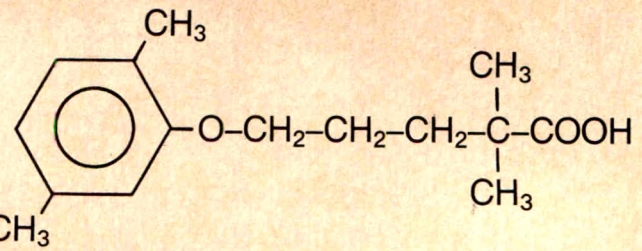

FIGURE 1. Gemfibrozil.

TABLE II Comparison of Gemfibrozil (1,200 mg/day) With Placebo in Increments of the HDL Cholesterol/ Total Cholesterol Ratio (% Change)

HLP Phenotype	Patients (n)		Change (%)	
	Gemfibrozil	Placebo	Gemfibrozil	Placebo
IIA	52	50	+33*	+3
IIB	46	55	+34*	+6
IV	106	100	+23*	+10

* $p < 0.05$, gemfibrozil versus placebo.
HDL = high-density lipoprotein; HLP = hyperlipoproteinemia.

gemfibrozil treatment, but that the decrease in VLDL synthesis might well be a major effect.

Most animal studies indicate that gemfibrozil reduces hepatic triglyceride production by inhibiting peripheral lipolysis and decreasing the hepatic extraction of plasma free fatty acids and also by inhibiting the synthesis of VLDL carrier apoproteins, a series of effects some of which gemfibrozil may share with nicotinic acid. In human studies by Vessby et al[7] performed several years ago, adipose tissue lipoprotein lipase was not affected by gemfibrozil therapy. We do not yet have good evidence that gemfibrozil exerts its primary effect by increasing lipolytic activity.

We have been trained to look at HDL from an epidemiologic point of view in a cross-sectional or longitudinal window of static measurement.[8–10] I propose that we start thinking about HDL from a pharmacologic point of view. Some of the lessons we have learned from the epidemiology of HDL are obviously applicable to its pharmacologic aspects, but perhaps there will be some surprises. There is an array of disparate agents, including diphenylhydantoin, terbutylene, estrogen, DDT, alcohol and insulin, that have all been demonstrated in experimental studies in man to increase HDL cholesterol (Table IV). Gemfibrozil, nicotinic acid and Dilantin® share top billing in elevating HDL levels. We obviously have a very disparate group of agents. Moreover, there is clearly no one-to-one relation between agents that reduce VLDL and agents that increase HDL (Table IV). Thus, alcohol allows a comparison with gemfibrozil (Table IV). Alcohol, in controlled human experiments, elevates HDL, but generally potently elevates VLDL at the same time. Gemfibrozil and nicotinic acid are similar in that they increase HDL and depress VLDL simultaneously. Diphenylhydantoin has the very potent effect of increasing HDL, probably similar to the effect of DDT in its direct effects on the liver. Terbutylene, a beta agonist, is associated with increased HDL levels, whereas propranolol, a beta-blocking agent, is associated with reduced HDL levels. The list of agents that affect HDL cholesterol is growing, and clearly these agents mediate their effects on HDL and VLDL in very heterogeneous ways. I propose that by studying these types of agents, we can learn much more about the pharmacologic aspects of HDL and their relation to coronary heart disease.

It may be useful to carry out the same exercise with agents that depress HDL (Table V). Probucol is a drug designed to decrease LDL cholesterol levels, which is a therapeutic attribute,[11–13] while at the same time it substantially reduces HDL levels. Oxandrolone and stanozolol, synthetic anabolic androgenic steroids, and natural or synthetic progestin, despite depressing VLDL and augmenting lipolysis, nevertheless, mediate a decrease in HDL,[14] instead of causing the expected increase in HDL levels, probably by increasing hepatic lipase levels. Conversely, at least several agents, particularly the beta-blocking drugs, which substantially decrease HDL levels (similar to stanozolol), are asso-

TABLE III Comparison of Gemfibrozil (1,200 mg/day) With Placebo in Reduction of Triglycerides and Increments in HDL Cholesterol

HLP Phenotype	Patients (n)		% Change TG		% Change HDL Cholesterol	
	Gemfibrozil	Placebo	Gemfibrozil	Placebo	Gemfibrozil	Placebo
IIA	52	50	−44*	+1	+25*	+1
IIB	46	55	−45*	+7	+20*	+8
IV	106	100	−40*	−7	+17*	+8

* $p < 0.05$, gemfibrozil versus placebo.
HDL = high-density lipoprotein; HLP = hyperlipoproteinemia; TG = triglyceride.

TABLE IV Metabolic Diversity of Agents That Increase HDL Cholesterol*

HDL Cholesterol	Up	VLDL Cholesterol Increase† or Decrease	LDL Cholesterol
Gemfibrozil	+++	+++	Down +
Nicotinic acid	+	+++	Down +++
Clofibrate	1/2+	+	Down/Up
Dilantin	+++	?	?
Estrogen	++	(+++)	Down
DDT	++	(+)	?
Alcohol	++	(++++)	?
Terbutylene	++	?	?
Insulin	+	+	Down

* Plus signs indicate relative strength of effect.
† Parentheses indicate an increase.
HDL = high-density lipoproteins; LDL = low-density lipoprotein cholesterol; VLDL = very low density lipoprotein cholesterol.

TABLE V Metabolic Diversity of Agents That Depress HDL Cholesterol*

HDL Cholesterol	Decrease	VLDL Cholesterol Increase or Decrease†	LDL Cholesterol
Probucol	+++		Down ++
Oxandrolone	+++	(++)	Up ++
Stanozolol	+++	(+)	Up ++
Progestins	+	(++)	Up +
Beta-blocking drugs	+++	++	Up +
Thiazide	++	++	Up 1/2+
Cortisone	++	++	Up ++
PCB	++	++	Up +
Kepone	++	++	Up +

* Plus signs indicate relative strength of effect.
† Parentheses indicate a decrease.
HDL = high-density lipoproteins; LDL = low-density lipoprotein cholesterol; VLDL = very low density lipoprotein cholesterol.

ciated with increased VLDL levels.[15] Therefore, when we look at the drugs and environmental agents that affect HDL, we have to keep in mind the very diverse effects of these agents on the other lipoprotein groups, and perhaps by analyzing these compounds we can learn much more about the pharmacologic aspects of HDL.

Gemfibrozil increases the levels of HDL and apo A-I, which are beneficial effects, we believe, and decreases the levels of VLDL, also putatively a beneficial effect.[16–19] HDL is a whole family of lipoproteins busily changing coats, giving off cholesterol and phospholipids and exchanging apolipoproteins C and E with VLDL. It is never in the same place at the same time. Obviously, therefore, we are discussing a flux of a family of molecules. We can speculate that the increased levels of HDL cholesterol or apolipoprotein A-I with gemfibrozil may reflect, in part, increased synthesis of apo A-I or apo A-II, or both, increased nascent HDL or increased total HDL cholesterol levels, which presumably would provide us with more nascent HDL or more HDL molecules available for reverse cholesterol transport, for interaction with prostaglandin prostacyclins, for transport of arachidonic acid and for all the antiatherogenic aspects that have been reported, and presumably that would be good (Table VI). Conceivably, gemfibrozil could reduce the catabolism of HDL and thus, although producing a cross-sectional increase in HDL, could actually reduce reverse cholesterol transport (Table VI). This possibility is very unlikely but needs to be examined. Dr. Moti Kashyap and I are researching the effects of gemfibrozil on I^{125}-HDL turnover, to study this area.

Oxandrolone and stanozolol, in comparison (Table VI), depress HDL cholesterol.[13,14] We know that they substantially increase the activity of hepatic lipase[14] and therefore severely depress HDL. We would think that epidemiologically this effect may not be good. If they possibly depressed synthesis of HDL and reduced the total number of molecules available to do their job, that effect might be bad (Table VI). However, it is very likely that these 2 drugs may well increase the catabolism of HDL,[14] increase the fractional catabolic rate of HDL and, thus, increase the flux of return of HDL to the liver, which could possibly be good (Table VI).

TABLE VI Pharmacologic Mechanisms (Speculative) for Effects of Drugs on HDL Cholesterol*

	HDL Cholesterol	HDL Synthesis	HDL Catabolism	VLDL Cholesterol
Gemfibrozil	Up	Possibly increased (good)	Possibly reduced (bad)	Down
Probucol	Down	Probably decreased (bad)	Possibly increased (good)	No change
Oxandrolone	Down	Possibly decreased (bad)	Probably increased (good)	Down, LDL
Stanozolol (LPL Up+, HL++)				Up cholesterol

* Plus signs indicate relative strength of effect.
HDL = high-density lipoproteins; HL = hepatic lipase; LPL = lipoprotein lipase; VLDL = very low density lipoproteins.

Finally, probucol depresses HDL cholesterol, and on the basis of Nestel's work[20] we think this depression reflects a probable decrease in the synthesis of HDL cholesterol.

In summary, we are in the infancy of the pharmacologic study of drugs and environmental factors that affect HDL. These drugs inevitably and necessarily affect other lipoprotein classes. It may well take us 15 to 20 or 25 years to provide evidence that pharmacologic intervention in HDL levels may also lead to amelioration of atherosclerosis, evidence that I believe is becoming increasingly apparent in the treatment of LDL levels.[21]

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Clinical Results With Gemfibrozil and Background to the Helsinki Heart Study

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The efficacy and safety of gemfibrozil in the treatment of dyslipidemia were investigated in a 6-year follow-up study of 254 patients with primary dyslipidemia. Most were middle-aged men with type IIA or IIB hyperlipoproteinemia. A significant correction in plasma lipid levels was seen in nearly 90% of all cases irrespective of the type of lipid abnormality. Overall, gemfibrozil therapy decreased levels of plasma total cholesterol 16%, triglycerides 45% and low-density lipoprotein (LDL) cholesterol 21%. The high-density lipoprotein (HDL) cholesterol concentration was increased 23%. The ratio of HDL cholesterol to total cholesterol increased from 0.13 to 0.20, approaching the value of matched controls in the population (0.23). Results in small pilot studies of patients with renal failure and uremia, the nephrotic syndrome or chemical diabetes were also encouraging. Plasma prekallikrein and kininogen values increased with gemfibrozil, possibly indicating correction of defective blood coagulation and fibrinolysis. Side effects were few; abdominal discomfort was noted in some patients and a skin rash in 2. In the intervention group, the number of myocardial infarctions was lower than expected (5 rather than 16). Results to date indicate that gemfibrozil effectively corrects most types of dyslipidemia, with minor side effects. The small number of observed myocardial infarctions supports the suggestion that an increase in HDL and a decrease in LDL levels during gemfibrozil therapy may be of clinical benefit in the prevention and management of coronary artery disease in subjects with dyslipidemia. The Helsinki Heart Study was designed as a definitive test of this hypothesis. This large, double-blind, placebo-controlled, primary (4,050 patients) and secondary (650 patients) prevention study is currently in progress.

After preliminary studies from several laboratories indicating the efficacy and safety of gemfibrozil in the management of hyperlipoproteinemia,[1] a major investigation involving a 6-month, placebo-controlled trial of 76 patients was initiated (Table I).[2] A total of 95 patients participated, but in 19 of them lipid values were controlled by the 3-month dietary instruction regimen preceding the study. Doses of 800, 1,200 or 1,600 mg/day of gemfibrozil were administered, and reductions in total cholesterol were achieved at each level. The 1,200-mg/day dose was deemed adequate from a clinical standpoint, for the additional benefit derived from the larger dose was small. Reductions in triglyceride levels were observed at all 3 doses, with the 1,200-mg/day dose providing a clinically satisfactory response. As a result, these patients were included in a long-term study using gemfibrozil at a dosage of 1,200 mg/day.

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During the design of this study in 1975, the importance of high-density lipoprotein (HDL) cholesterol was not apparent. When it did become known, treatment was stopped in 51 patients. These subjects were followed up for 6 months, during which time their mean total cholesterol levels increased significantly (17%), whereas their mean HDL cholesterol levels decreased (−20%). It took 3 to 4 months for the gemfibrozil effect to stabilize. When treatment was reinstated, total cholesterol, HDL cholesterol and the HDL/total cholesterol ratio soon reached previous treatment values. These levels have subsequently been sustained for 3 years.

A total of 254 patients with type IIA and type IIB dyslipoproteinemia, mostly from the county of North Karelia but including some persons from Helsinki, were treated during the last 7 years. Gemfibrozil therapy produced a 16% reduction in mean total cholesterol, a 23% reduction in low-density lipoprotein (LDL) cholesterol, a 23% increase in HDL cholesterol and a 45% decrease in triglyceride levels (Table II). Plasma lipid values during gemfibrozil therapy were close to those in a matched reference group. Interestingly, the HDL/total cholesterol ratio, which was low in the be-

TABLE I Six-Month, Placebo-Controlled, Double-Blind Trial of Increasing Dosage*

	Placebo Group		Gemfibrozil Group	
Patients (n)	38		38	
Sex	Male		Male	
Mean age	44.6		45.6	
Type IIA	15		15	
Type IIB	23		23	
Serum cholesterol (mmol/liter)				
Baseline	8.38		8.36	
800 mg/day/8 wk	8.46	(+1%)	7.50	(−10%)
1,200 mg/day/8 wk	8.31	(−1%)	7.20	(−14%)
1,600 mg/day/8 wk	8.17	(−2.5%)	7.02	(−16%)
Serum triglyceride (mmol/liter)				
Baseline	2.02		2.12	
800 mg/day/8 wk	2.05	(+1.5%)	1.45	(−32%)
1,200 mg/day/8 wk	2.01	(±0)	1.26	(−41%)
1,600 mg/day/8 wk	2.13	(+5%)	1.05	(−50%)

* Differences in serum cholesterol and triglyceride levels caused by gemfibrozil are significant at the $p < 0.001$ level in all instances. Of a total of 95 patients, 19 were controlled by the diet alone and were not included in the drug treatment group. To convert cholesterol and triglyceride values to milligrams per deciliter, multiply by 38.7 and 88.5, respectively.

TABLE II Overall Assessment of Gemfibrozil Efficacy in Correcting Primary Dyslipidemia in Middle-Aged Male Subjects

	Gemfibrozil		Control
	Before	After	
Total cholesterol (mmol/liter)	7.22 ± 0.8	6.04 ± 0.7 (−16%)	5.5 ± 0.9
HDL cholesterol (mmol/liter)	0.97 ± 0.25	1.22 ± 0.29 (+23%)	1.30 ± 0.30
HDL/total cholesterol	0.13	0.20	0.23
Triglycerides (mmol/liter)	2.12 ± 0.6	1.10 ± 0.5 (−45%)	1.0 ± 0.4

HDL = high-density lipoprotein.

TABLE III Effect of Gemfibrozil on Apolipoproteins A-I and A-II in 17 Male Middle-Aged Dyslipidemic Subjects (IIA or IIB)

	Apo AI (mg/dl)	Apo AII (mg/dl)
Placebo		
Initial	128.4 ± 26.8	35.6 ± 4.7
3 mo	129.2 ± 21.6	36.4 ± 4.9
Gemfibrozil		
1 mo	142.6 ± 31.3*	40.0 ± 5.6†
2 mo	138.9 ± 22.9‡	38.4 ± 4.1*
4 mo	145.2 ± 39.3*	39.6 ± 5.8*

* $p < 0.01$.
† $p < 0.05$.
‡ $p < 0.001$.

ginning, increased to a level close to that seen in the reference group. With certain reservations, this ratio may be the most reliable single practical parameter that can be used to indicate the degree of cardiovascular risk associated with dyslipidemia.

In more recent studies (so far mostly unpublished), we found that during gemfibrozil treatment, both major HDL apoproteins, apo A-I and apo A-II, are significantly increased (Table III). Similar confirmatory observations were reported elsewhere.[3,4] In a group of 12 male patients, both HDL_2 and HDL_3 subfractions were significantly increased during 3 months of gemfibrozil treatment[5] (Table IV). The absolute change in HDL_2 cholesterol was 0.1 mmol/liter and the change in HDL_3 0.2 mmol/liter. However, when these changes are expressed as percentages, they are greater in HDL_2 because its initial levels were low. The same plasma samples were analyzed in 2 different and independent laboratories using somewhat different techniques. The interlaboratory variation was practically negligible, strongly suggesting that such changes were real despite the small patient sample. Without complicated kinetic studies it is not possible to understand fully the mechanisms leading to increases in these HDL subfractions. However, it seems likely that in essence, HDL_3 synthesis is increased in the liver and, as a result of an increase in catabolic rate, more HDL_2 is formed.[5,6] Most investigators have found the strongest correlation between low HDL_2 levels and coronary artery disease.[5,7]

In a study of 60 subjects with dyslipidemia and previous myocardial infarction, the antidyslipidemic efficacy of gemfibrozil was similar to that reported for patients free from myocardial infarct.[8] In a pilot study of patients with renal failure and uremia or the nephrotic syndrome, response to gemfibrozil was good without drug-attributable side effects.[9,10] Results of studies in

TABLE IV Effect of Gemfibrozil on Serum High-Density Lipoprotein Subfractions*

	TG	TC	HDL-TC	HDL_2-C	HDL_3-C	HDL_2/HDL_3
Basal						
Mean	2.12	6.66	1.18	0.25	0.93	0.27
±SD	0.90	0.53	0.25	0.13	0.17	. . .
Gemfibrozil						
Mean	1.02†	5.63†	1.49†	0.34‡	1.15†	0.30
±SD	0.35	0.69	0.37	0.20	0.20	. . .
mmol/liter	−1.10	−1.03	+0.31	+0.09	+0.22	. . .
%	−51.9	−15.5	+26.2	+36.5	+23.7	. . .

* Prospective study with previously nontreated subjects (n = 12); precipitation-based technique.
† $p < 0.001$.
‡ $p < 0.005$.
C = cholesterol in various fractions; HDL = high-density lipoprotein; SD = standard deviation; TC = total cholesterol; TG = total triglycerides.

patients with chemical diabetes were also promising,[11–13] in that there was a clear-cut increase in HDL cholesterol and a decrease in triglyceride levels. Most patients were receiving dual therapy with gemfibrozil and tolbutamide.[13]

Gemfibrozil has been found to consistently increase both plasma prekallikrein and kininogen values.[14] Changes in the levels of HDL cholesterol and prekallikrein and in the levels of apoprotein A-I and kininogen correlated significantly. These changes in prekallikrein and kininogen are difficult to interpret, but they are consistent with a correction in impaired blood coagulation or fibrinolysis, or both.[15,16] With the recent finding of a high incidence of thrombi during the acute phase of myocardial infarction,[17] the current observations warrant further investigation.

During gemfibrozil administration no serious adverse reactions attributable to the use of the drug were seen in erythrocyte sedimentation rate, hematology, blood sugar or hepatic or renal function. Ophthalmologic examination did not indicate any organ damage. Gastrointestinal complaints, such as stomach pain and swelling, were somewhat more frequent among patients on active therapy compared with those taking placebo. Two patients had eczema, most likely attributable to gemfibrozil. Eleven had the drug withdrawn because of abdominal discomfort and 5 because of transiently elevated transaminase levels possibly due to alcohol consumption. Other dropouts resulted from nonresponsiveness to therapy, from moving out of the area or most often from the difficulties of frequent clinical visits in a rural area involving return distances of up to 90 miles.

No adverse drug interactions were observed between gemfibrozil and thiazides, furosemide, digoxin, beta-adrenergic blocking drugs, common spasmolytics, benzodiazepines or acetylsalicylic acid.

Helsinki Heart Study

Once clinical studies with adequate numbers of patients had confirmed the safety and efficacy of gemfibrozil in the management of most common types of dyslipidemia, our subsequent concern was to determine whether gemfibrozil therapy merely brought lipid levels to normal or whether it also offered some clinical benefit such as a reduction in cardiac events. According to statistical analyses, the expected number of myocardial infarctions in our treatment group was 16.[2] The lower incidence of 5, 1 of which occurred at the start of therapy and 1 in a patient who consistently failed to take the drug, encouraged us to undertake a placebo-controlled, prospective, double-blind study to test the assumption that correction of lipid abnormalities would reduce the risk of coronary heart disease and myocardial infarction.

With approval of the management and trade unions of the participating institutions, the Ethical Committee of the University of Helsinki and the Finnish National Board of Health, the Helsinki Heart Study was instituted under the supervision of an International Advisory Council chaired by Professor E. A. Nikkila. The Advisory Council consists of experts in metabolic disease, cardiology, biostatistics, epidemiology and chemical pathology and also contains the principal medical officers of the participating institutions together with representatives from Warner-Lambert Clinical Research (U.S.A. and U.K.). All Finnish members of the Advisory Council will constitute a Watch Committee responsible for ethical aspects in the continuation or termination of the study.

The study parameters were initially planned and calculated for a primary prevention study only (Table V). The secondary prevention group is a byproduct of the screening for the primary prevention study, as reflected by its size. However, because of the higher event rate, even the secondary prevention group should form the basis for a meaningful study.

All male employees aged 40 to 55 years from the Finnish Railways (8,000), Finnish Post and Telecommunication System (7,600) and 5 industrial companies (8,000) were invited to participate. From the total of 23,600 eligible men, 83% were willing to volunteer for the initial screening, which included analyses of total and HDL cholesterol levels and data on their general health and medical history. On the basis of the selection criteria of total low-density lipoprotein (TLDL) cholesterol (total minus HDL cholesterol), which had to be $\geq$5.2 mmol/liter, 7,000 men (30%) were admitted for the second screening, which included careful physical examination, electrocardiography, plasma lipid determinations (including triglycerides) and blood chemistry analyses. All lipid analyses have been and will continue to be performed in the same laboratory.

From this group, 4,700 men were eligible and willing to volunteer, 4,050 (17%) for the primary and 650 (2.7%) for the secondary prevention study. For final acceptance into the study, the volunteers had to have a TLDL cholesterol value of $\geq$5.2 mmol/liter, measured on 2 consecutive occasions 6 to 8 weeks apart. Such patients also had to be free from other major illnesses, but stable mild hypertension and chemical diabetes were not criteria for exclusion. Patients with coronary heart disease at entry were eligible for inclusion in the secondary prevention study (Table VI).

The investigation is a double-blind, placebo-controlled study in which half of the patients have been randomly assigned to active medication (gemfibrozil, 600 mg twice daily) and the remainder receive a matching placebo. Before allocation to treatment, patients in the secondary prevention group were stratified

TABLE V Parameters of the Helsinki Heart Study (Primary Prevention)

Parameter	Value
1. Study period	5 yr
2. Total dropout rate	20%
3. Annual placebo incidence of coronary heart disease events	1.5%
4. Reduction of coronary heart disease events (gemfibrozil versus placebo)	30%
5. Power (β = 10%)	90%
6. Level of significance (α)	1%
7. Number of men needed to meet these requirements	4,000

TABLE VI Number of Characteristics of Patients Enrolled in the Helsinki Heart Study*

Primary Prevention	Secondary Prevention
4,050 men	650 men
Age: 40–55 years at entry	Age: 40–55 years at entry
TLDL† ≥ 5.2 mmol/liter	TLDL ≥ 5.2 mmol/liter
No evidence of coronary heart disease	Evidence of coronary heart disease (ECG, history)
	Stratification for severity of coronary heart disease, age and smoking habits
Random allocation for gemfibrozil (1,200 mg/day) or for matching placebo	Random allocation for gemfibrozil (1,200 mg/day) or for matching placebo

* There will be clinical visits at 3-month intervals for 3 to 5 years. Endpoints will be either myocardial infarction or coronary death.

† TLDL = total cholesterol minus high-density lipoprotein cholesterol.

TLDL = total low-density lipoproteins.

for severity of coronary heart disease (previous myocardial infarction or history of angina), smoking habits and age. All patients will have clinical visits at 3-month intervals up to 5 years. The end points will be myocardial infarction or coronary death.

All patients will receive health education and will be prescribed a theoretically optimal diet. Because there are suggestions that dietary and biobehavioral modifications may themselves be effective to some degree,[18] pharmacotherapy alone was rejected on ethical grounds. Thus, the study should indicate any possible increase in protection against coronary events provided by gemfibrozil therapy over that provided by biobehavioral management alone. The study began in January 1981 and patient enrollment was completed in June 1982, with the exception of 90 patients in the secondary group enrolled in early November 1982. The investigation is in progress and is scheduled to last 5 years. Progress reports will be published at intervals.

Comments

The Helsinki Heart Study focuses on individuals at high risk for coronary heart disease so as to avoid difficulties of analysis due to concurrent illness, advanced age or dilution by low-risk individuals. As calculated from different sources and adjusted to the 1981 level, the annual mean myocardial infarction rate for Finnish men aged 50 years (mean age of the enrolled patients) is 10 per 1,000.[19,20] The incidence of coronary heart disease has been declining. However, the current decline has not solved the problem or removed the need for further attempts to improve the management of patients with coronary heart disease. Genetically, Finns are homogeneous, in essence 1 nation of 5 million inhabitants with the same hereditary origins. In contrast to some other countries, notably the United States, Finns aged ≥40 years also have a settled and stable lifestyle. In addition, most are concerned about their health. Thus, Finnish men should form a good group for a major prevention study on coronary heart disease, and almost 5% of the entire eligible male population (aged 40 to 55 years) has been screened.

Of the study parameters (Table V), the greatest errors may occur in the anticipated placebo incidence of coronary heart disease, which may not be as great as expected, and in the reduction of coronary heart disease events by gemfibrozil, which, in contrast, may be higher than predicted. With 1 year's results available from two thirds of the patients in the primary prevention group, it is already clear that the initial total cholesterol (7.7 mmol/liter, or 298 mg/dl) has decreased some 10% in the entire group (Dresner AJ, personal communication, 1982), suggesting a significant change in cholesterol values in patients on active treatment. Our main concern is to maintain scientific interest and enthusiasm among both staff and patients in a long-term study designed to solve a major medical problem.

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Clinical Results With Gemfibrozil

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Gemfibrozil has been found to increase high-density lipoprotein (HDL) cholesterol levels in both animal and clinical studies. Although a reduction in saturated fat intake and a concurrent increase in unsaturated fat intake may reduce low-density lipoprotein (LDL) cholesterol values, the only dietary modification known to increase HDL is that resulting from significant weight loss. The Framingham study showed that the risk associated with HDL cholesterol (lower values, higher risk) is independent of the risk relative to LDL cholesterol (higher values, higher risk).

A multicenter trial in the United States showed a reduction of elevated serum triglyceride levels by more than 40% and of cholesterol to normal or by 20% in 50% of patients who received gemfibrozil, versus 25% of those who received a placebo. Gemfibrozil therapy reduced elevated serum very low density lipoprotein levels concurrently with triglyceride levels. It also increased serum HDL by approximately 20% and the HDL/total cholesterol ratio by approximately 30%. HDL cholesterol levels continued to increase for up to 2 years in the multicenter study. The increase over baseline levels was seen in all 3 types of hyperlipoproteinemia (IIA, IIB and IV).

The most common side effects were minor gastrointestinal symptoms and transient abnormalities in hepatic enzymes, which occurred in less than 3% of the patients. There were no other liver function abnormalities and no evidence that gemfibrozil induced liver toxicity. Gemfibrozil had a safety advantage over clofibrate, especially with regard to lithogenic potential. Gemfibrozil demonstrated a low side-effect profile and a positive influence on regulating lipoprotein levels in patients with hypercholesterolemia and hypertriglyceridemia.

The Multiple Risk Factor Intervention Trial has shown some of the limitations of environmental modifications of high-density lipoprotein (HDL) in that only a 2- or 3-mg/dl change (about 7 to 10%) has been achieved by 3 environmental modifications: (1) an increase in intake of alcohol, (2) a reduction of 10 pounds or more in body weight and (3) cessation of smoking. This study, which was designed to modify nutrition, lower cholesterol levels, modify smoking behavior and control cholesterol, did not have a component of exercise modification. Because of these limitations, our attention was then directed to the pharmacologic modification not only of total serum cholesterol, but also of HDL, and we, like others, have used gemfibrozil for this purpose.

This compound is similar to clofibrate but differs in potency, mechanism of action and therapeutic effects. The multicenter study of this compound involved 427 patients who primarily had type II hyperlipidemia; 215 had type II hyperlipidemia, with 108 of those having IIA and 107 having IIB. The remaining 212 had type IV hyperlipidemia. The mean lipid levels for those with IIA were: cholesterol 323 mg/dl and triglycerides 135 mg/dl. The principal results of treatment of this group were a reduction in cholesterol of approximately 5.4% in a 6-month-long trial and an increase in HDL of 22%. Those with type IIB had a mean cholesterol level of 318 mg/dl and a mean triglyceride level of 237 mg/dl. The mean cholesterol reduction in this group was 6.9%; triglycerides decreased markedly by 41%, and HDL increased 17%. The type IV group had a primary elevation in triglycerides. The mean triglyceride level was 319 mg/dl. They had only a modest decrease in cholesterol of 2%, whereas triglycerides decreased markedly and HDL increased substantially, about 24%.

These changes were compared with those from placebo, in which the changes in cholesterol were very brisk in the type II group and minimal in the type IV, as would be expected in that the type IV group had only a modest elevation in cholesterol (Table I). Similarly, an effect on triglyceride was noted both in the multicenter trial and in other protocols used for testing the effect of gemfibrozil on these 3 types of hyperlipidemia (Table II). Finally, the HDL cholesterol increased to its greatest degree in patients with type IIA and to a lesser

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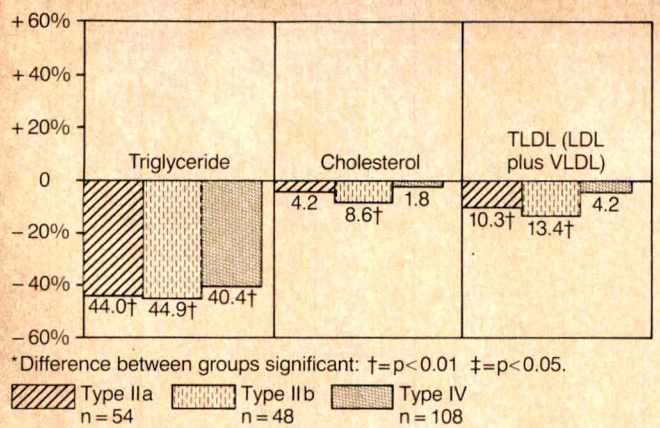

FIGURE 1. Summary of results with Lopid® in controlled phase of multicenter study—average percent change from baselines at recommended dosage of 1,200 mg/day. LDL = low-density lipoproteins; TLDL = total low-density lipoprotein; VLDL = very low density lipoproteins.

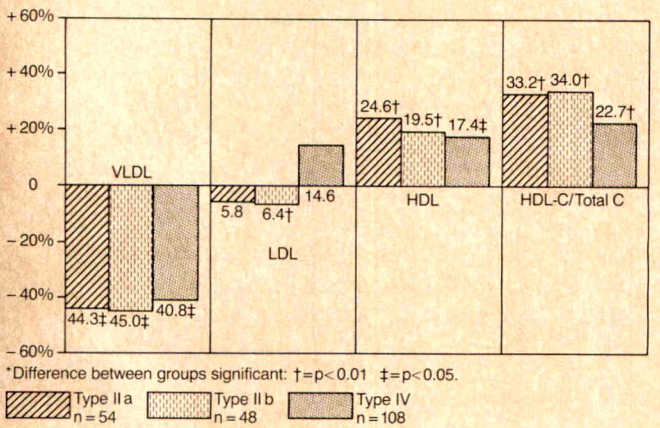

FIGURE 2. Summary of results with Lopid® in controlled phase of multicenter study. Average percent change from baselines at recommended dosage of 1,200 mg/day. C = cholesterol; HDL = high-density lipoproteins; LDL = low-density lipoproteins; VLDL = very low density lipoproteins.

degree with type IIB and type IV, but in all 3 groups there was a significant increase in HDL compared with placebo (Table III).

These results (Fig. 1 and 2, Tables I, II and III) show a decrease in triglycerides at a dose of 1,200 mg/day by type of hyperlipidemia, a modest decrease in cholesterol and a small decrease in total low-density lipoprotein (TLDL) (low-density lipoproteins [LDL] plus very low density lipoproteins [VLDL]), showing that most benefit was derived from the reduction in triglycerides (Fig. 1). As VLDL and LDL decreased, HDL increased and with this the ratio of HDL to total cholesterol improved (Fig. 2). This shows the effect of change with time in which the LDL decreased early and stayed down in all groups but tended to decrease even later after 10 months of administration, primarily in those with type

TABLE I Effects of Lopid® (1,200 mg/day) and Placebo on Serum Triglycerides

Protocol number	Type	% Change	
		Lopid	Placebo
Multicenter	IIA	−44.0	+1.2
	IIB	−44.9	+7.4
	IV	−40.4	−7.1
719-39	IIA	−51.2	−4.2
	IIB	−38.8	+3.9
719-47	IIA	−37.9	+10.5
	IIB	−43.7	+0.8
	IV	−44.5	+14.9

TABLE II Effects of Lopid® (1,200 mg/day) and Placebo on Total Low-Density Lipoprotein Cholesterol Level (Multicenter Study)

Type	% Change	
	Lopid	Placebo
IIA	−10.3	−1.2
IIB	−13.4	+2.4
IV	−4.2	−1.2

TABLE III Effects of Lopid® (1,200 mg/day) and Placebo on High-Density Lipoprotein Cholesterol Level (Multicenter Study)

Type	% Change	
	Lopid	Placebo
IIA	+24.6	+1.3
IIB	+19.5	+8.0
IV	+17.4	+8.2

IIA. The HDL increased in groups, and again those with type IIA had the most beneficial late effect, with a peak at 5 months and then a secondary peak after 9 months.

There was a minimal change in glucose tolerance in that the group that received gemfibrozil had a somewhat higher level of blood glucose after glucose load when compared with those on placebo. The side effects with this drug were minimal, the most common being abdominal pain, and that was only slightly different from placebo; this abnormality was found in 3.8% of the gemfibrozil-treated patients versus 3.3% of those with placebo. Diarrhea was more common in the placebo group; epigastric pain was almost as common when compared with patients who received gemfibrozil. Therefore, we concluded that the administration of gemfibrozil markedly reduced the level of serum triglycerides and more moderately decreased the level of serum cholesterol. The drug was well tolerated. However, the level of blood sugar may increase, and it must be monitored.

Discussion—Effects of Pharmacologic Intervention on High-Density Lipoproteins

ANTONIO M. GOTTO, Jr., Moderator

Dr. Alan Howard (Cambridge, England): I would like to ask Professor Manninen a question about this new study that started in 1981. I notice that your exclusion point is greater than 5.2 low-density lipoproteins (LDL). Now gemfibrozil has only a modest effect on LDL. We have just seen that it lowers LDL by only 10%. Wouldn't it have been far better to look at people with either low levels of high-density lipoproteins (HDL) or high levels of very low density lipoproteins (LVDL), because these are the people you are actually going to be treating. It may be that you set up your experiment in such a way that you are studying the wrong population.

Vesa Manninen (Helsinki, Finland): That is a very good question and I really do not know how to answer it. Before we made a decision about the lipid parameter, we had lengthy discussions with experts on biometrics and with epidemiologists. We decided to have 1 single parameter, which was that the LDL cholesterol should be 5.2 or higher on 2 consecutive measurements; but of course there are arguments against this.

Dr. Gotto: I would like to ask 1 question of the investigators who have worked with gemfibrozil. Several points have been made concerning a comparison between this drug and clofibrate. The drug is not halogenated. I wonder if you have data on whether gemfibrozil produces a lithogenicity of the bile that is seen with clofibrate. Have you observed an increased incidence in gallstones? Thirdly, have the effects on the induction of peroxisomes, similar to the effects seen with clofibrate, been looked for with gemfibrozil?

Dr. Manninen: In our studies, we have not noted any problem with gallstones. The literature shows that gemfibrozil may be less lithogenic than clofibrate, and the data presented show that. These studies have been on healthy volunteers, and I think Dr. Marcus may know more about them.

Ed Marcus (Warner-Lambert, Morris Plains, New Jersey): As a physician I did some work in the United States with the 427 subjects whom Dr. Pickering referred to, and we were interested in the possible development of gallstones in these patients. Therefore, on baseline, before admission, we did cholecystograms; usually oral, in each of these subjects, eliminating from the study those with stones, and proceeded to reevaluate annually those who remained in the study. Our incidence of new gallstone formation at the end of 1 year was approximately 1.5%, and at the end of 2 years an additional 1% of the subjects developed evidence of either new gallstones where none had appeared previously or a considerable enlargement of minuscule or small stones that were present earlier. Whether this represents a lithogenic potential comparable to that of clofibrate I cannot say. It may well be that gemfibrozil has only limited lithogenic potential.

Dr. Gotto: Thank you. Dr. Little.

J. Alick Little (Toronto, Ontario, Canada): One problem I am presented with quite often when dealing with patients with marked hypertriglyceridemia who have already had pancreatitis is in prescribing a drug that may be either lithogenic or associated with increased pancreatic disease, as in the coronary drug trials. Has anyone had any experience with prescribing this or related drugs to patients who have already had pancreatitis?

Dr. Gotto: Dr. Lewis?

Barry Lewis (London, England): I would take the opposite view that one clear indication for this group of drugs is a patient with severe endogenous hypertriglyceridemia who has already had or has the risk of acute pancreatitis.

I think the structure of the symposium has caused many of us to be rather more speculative than we would have liked. I wonder whether I could pose a question I think might be of practical importance to us, namely, what would the panel feel are the indications for the CPIV group of drugs: severe hypertriglyceridemia, a type III, more generally for hyperlipidemia?

Dr. Gotto: Thank you. Professor Paoletti, shall we start with you?

Rodolfo Paoletti (Milan, Italy): The question is, what are the indications of the CPIV-related drugs? I think we have to postpone a final reprise of this question until we know how they affect arterial lesions. In this symposium will be presented some of the first studies showing that drugs like fenofibrate and nicotinic acid combined may cause regression in human femoral arterial lesions in a fairly short time. I refer to the preliminary work of Dr. Olsson in Sweden, for instance, and a study like this can easily be repeated for a number of drugs. We have 2 purposes: to assess the efficacy and to compare drugs with completely different modes of action. Until the preliminary part of the study is terminated, we are in no position to assess which drug is the best for which type of lipid or arteriosclerotic high-risk condition.

Dr. Gotto: Dr. Glueck, what are your indications?

Charles J. Glueck (Cincinnati, Ohio): I agree with Professor Paoletti's comments, but one then faces the conundrum of waiting to institute therapy until all the data are in relative to these specific agents. I believe that individuals who had severe primary depression of HDL cholesterol and/or atherosclerosis and a strong family history of atherosclerosis would not respond to environmental modifications. I certainly think that the use of gemfibrozil- or bezafibrate-type drugs that might raise HDL significantly would be appropriate, but without any conclusion about the antiatherogenic effect. We obviously do not have the data. In individuals who have substantial endogenous hypertriglyceridemia coupled with less than the tenth decile HDL cholesterol, who are unwilling or

unresponsive to diet or weight loss and who also have a strong family history of heart disease, you could make a reasonable case for carefully controlled intervention, again with the same caveat. We do not yet have any data, short of some of Dr. Blankenhorn's preliminary data with nicotinic acid, suggesting that such drugs reverse or retard the progression of atherosclerosis. However, I think there is a reasonable belief that such things might occur, and there are enough preliminary data of the type Dr. Blankenhorn produced in his studies—the type that Dr. Paoletti referred to—that in those 2 types of individuals the indication for treatment would be available. One could ask the same question about LDL. Do we yet have smoking-pistol evidence that primary prevention and lowering of LDL will ameliorate coronary heart disease in atherosclerosis? I suggest the answer to that is, not yet. Yet, I also suggest that most of us, when faced with men who have primary elevations of LDL and in whom diet alone will not work, are using drugs.

Dr. Manninen: My view is that we start with health education. We need more effective methods to change a nation's or an individual's habits. We cannot do that in a short period of time; it would take decades. Perhaps we do not have a basis for changing those habits too drastically. We have to start with these advances in health education and then if we have patients who do not respond to them, we can do something for them. The category we have forgotten includes the young and middle-aged individuals with type IIB who are at the highest risk. They have elevated LDL, elevated VLDL and low HDL. I believe we should have a fresh look at the treatment in these patients.

J. Edward Pickering (Philadelphia, Pennsylvania): To the degree we believe in the hazards of risk factors, we have to make quantitative changes to bring people to low-risk status. So far, we have not been able to do that with a large enough number of people with the Multiple Risk Factor Intervention Trial, and for those reasons we have an interest in pharmacologic modification.

Oli Fergamen (Denmark): In the back of all our minds are the problems posed by the WHO clofibrate study and the very serious side effects that seem to be engendered by long-term treatment with clofibrate. However, another development in the last year that we have not mentioned up to now is the results of the Oslo diet-cigarette study. The Oslo group demonstrated a 45% reduction over 5 years in sudden death or acute myocardial infarction, fatal and nonfatal, in some 600 men between the ages of 40 and 49 years who were in the high-risk group as defined by cholesterol levels. When that study is taken into consideration, as you must when designing large drug studies, you get some idea of the relative worth of pharmacologic versus dietary reduction of lipids. I am sure the Helsinki Heart Study was planned long before the results of the Oslo Heart Study were in, but I would be very interested to hear what kind of considerations Dr. Manninen and his colleagues were forced to make after the results of the Oslo Heart Study came out.

Dr. Gotto: Dr. Manninen, do you or Dr. Nikkila want to respond to that question? Have you made any modifications in your basic plan as a result of the Oslo Heart Study?

Esko A. Nikkila (Helsinki, Finland): I think not, because what we tried to look for in this study was the effect of a drug. As Dr. Manninen already mentioned, we just wished to study the effect of reducing the LDL and increasing HDL. We did not screen the triglycerides, but we just screened the difference between the total and the VLDL.

Dr. Rifkind (Rockville, Maryland): I would like to comment on the response to the question about therapy of subjects with hypolipidemia. Certainly, there is a dilemma in encountering a high-risk subject with hyperlipidemia and wondering what one should do for him. The temptation is always to say, since the patient is at high risk, we'll use the latest agent available that may have some efficacy. But I remind myself that we have a whole series of drug hyperlipidemic studies behind us that have given rise to a series of toxic problems; for example, the Coronary Drug Project in high-dose and low-dose estrogen, the Coronary Drug Project in the use of dextrothyroxine and subsequently with clofibrate and then the WHO clofibrate study. They have all shown that the toxic problems have to be weighed against possible and as yet unproved benefits. I caution the group on advocating the use of hypolipidemic drugs until we have the results of systematic studies such as the Helsinki study. As far as the comment about the pressure to use drugs because environmental modifications take a long time, I would like to echo the comment made by the previous speaker. I hope to show in my own presentation that if we look at the results of a large number of dietary studies—especially when we contrast them with a variety of lipid studies, the dietary studies are generally effective and sometimes surprisingly effective in lowering cholesterol, and broad-scale lipid studies are generally ineffective or at best disappointing.

Dr. Gotto: The problem is that we just do not have safe and effective drugs for lowering cholesterol by 30 or 40%. If we had such drugs, then it probably would not take hundreds of millions of dollars, thousands of subjects and years of study to try to answer these questions.

Sanders Williams (Durham, North Carolina): Dr. Manninen presented some interesting data and alluded to some effects on fibrinolysis. Have you taken direct measurements of fibrinolytic activity in response to gemfibrozil?

Dr. Manninen: No, we have not. That is speculation to speak about this correction of defective fibrinolyzers.

Dr. Williams: Yes, I agree. It is a very interesting speculation.

Dr. Manninen: However, the speculation is based on similar findings with clofibrate, and I believe that Calvalio in Boston has really achieved similar results with clofibrate.

Dr. Marcus: I want to respond to the chairman's request for some information about peroxisome changes in human subjects. An article by Dr. Felix de la Iglesia in the current issue of *Atherosclerosis* addresses this problem or the situation. We have studied 9 patients who have had gemfibrozil for up to 3 years, and subjects with liver biopsy did not show any of the peroxisome changes that were seen in male rats. This finding simply indicates our concern and interest in showing that there are differences in the 2 species.

Günter Schlierf (Heidelberg, West Germany): My remark will be very brief and addresses the question of indications for drugs. I think it depends on the risk you want to treat. The primary prevention study of Dr. Oliver was a study in which the lipid-lowering drug was used in people who did not have real hyperlipidemia, so there were side effects in all of them. Therefore, I essentially agree with Dr. Lewis. If we have subjects with hyperlipidemia, the indication is for lipid-lowering drugs in particular, compared with other risk factors. We have to look at the side effects. Some drugs have fewer side effects, and when we know them we can decide which drugs to use.

Manheim (Manheim, Germany): I have a question for Dr. Paoletti. You indicate that changes in apolipoproteins A1 and A2 with bezafibrate might indicate an increase in HDL_3 rather than in HDL_2. There is direct evidence by Professor Schwein in Munich that, in using the preparative ultracentrifuge, HDL_2 increases rather than HDL_3. Nevertheless, if you assume an increase in HDL_3, what mechanism would you propose? You also showed that the major mode of action of this drug is an increase in lipolytic activity.

Dr. Paoletti: I tend to believe that the mode of action of the drug is exerted mainly on the lipolytic activity, and the effects on the HDL_2 and HDL_3 are probably not an essential part of the mode of action. Unfortunately, the data available even in animal studies do not explain sufficiently clearly how the HDL in synthesis or formation is increased. Is this a direct mechanism or an aspecific mechanism? However, I would like to remind everyone that the list of drugs that affect HDL is extremely long and includes agents such as dioxin, which are pollutants. Certainly we do not necessarily have to find the mode of action for important drugs acting against atherosclerosis essentially in the formation or accumulation of HDL.

Dr. Gotto: I would like to reemphasize the great heterogeneity of the HDL subfractions. We have simplified them today by calling them HDL_2 and HDL_3, but there certainly are further subfractions. Dr. Patsch in Houston has shown that HDL_3 is clearly divided into at least 2 subfractions. We know there are at least 4 different sources. We do not know the sites of catabolism of HDL, and so there are multiple sites where drugs, exercise and diet can affect different sources of HDL and different subfractions.

Dr. G. Michael B. Berger: (Capetown, South Africa): I would like to go right back to Dr. Little's question about the treatment of hypertriglyceridemia, at least for acute pancreatitis. Very briefly, in our experience almost invariably the hypertriglyceridemia that causes pancreatitis of the severe exogenous type responds extremely well to a very low fat diet if you can obtain compliance, and it does not respond to drugs such as clofibrate. This response even applies to patients with hyperchylomicronemia unassociated with low lipoprotein lipase activity.

Dr. Gotto: Yes. Dr. Glueck and others have also shown that oxandrolone and the progestational agents such as norethindrone acetate are effective in exogenous hyperlipidemia.

I would like to express our gratitude to Parke-Davis and Warner-Lambert for making this symposium possible.

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1/LOWERS elevated serum levels of triglyceride-rich VLDL and, to a lesser extent, cholesterol-rich LDL (very-low- and low-density lipoproteins implicated in dyslipidemia)

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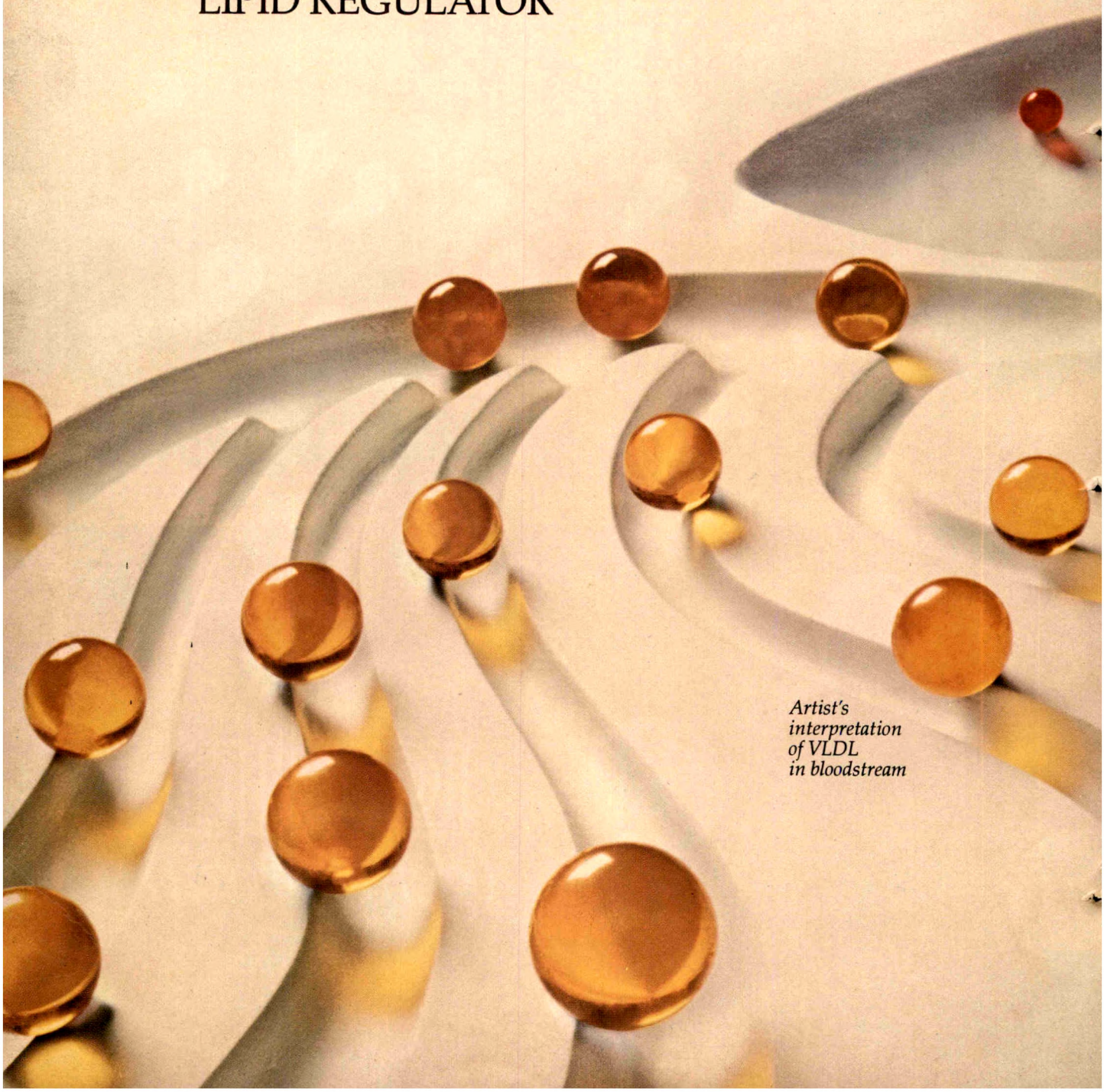
LOPID is indicated for treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet.



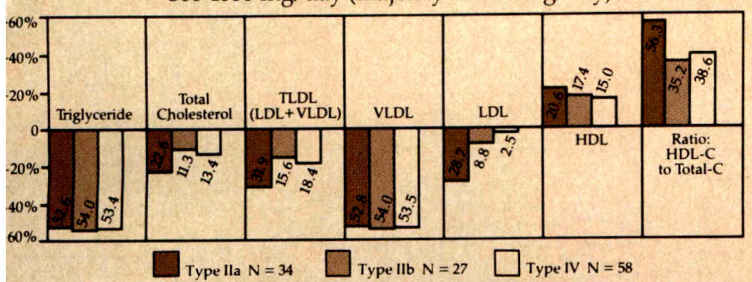
Artist's interpretation of VLDL in bloodstream

12.1.84

Lipid-regulating efficacy demonstrated in 1,437 patients with dyslipidemia[1]

Results of open-label phase of US multicenter study (119 patients) at end of 12 lunar months*

Average % change from baseline at doses ranging from 800-1600 mg/day (majority at 1200 mg/day)†



*Visit every 4 weeks during long-term use of LOPID.

†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

Well tolerated, well accepted in clinical trials[1]

Profile of side effects similar to that of placebo.

No significant abnormalities seen in clinical and laboratory evaluations.

Less than 1% patient dropout in largest US study.

Convenient BID dosage

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

Reference:

1. Data on file, Medical Affairs Dept, Parke-Davis.

Artist's interpretation of HDL in bloodstream

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A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (See WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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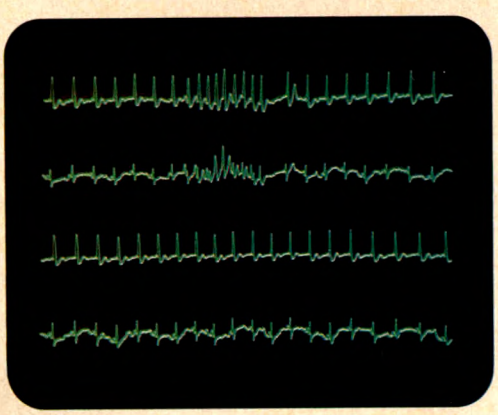

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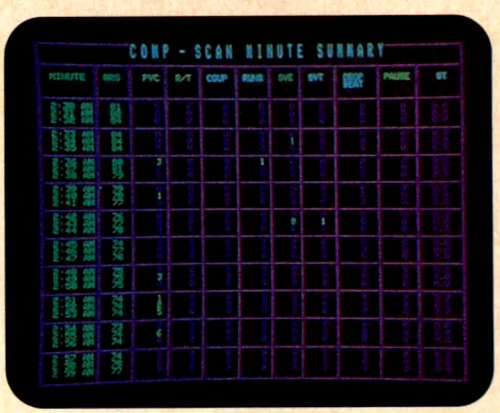

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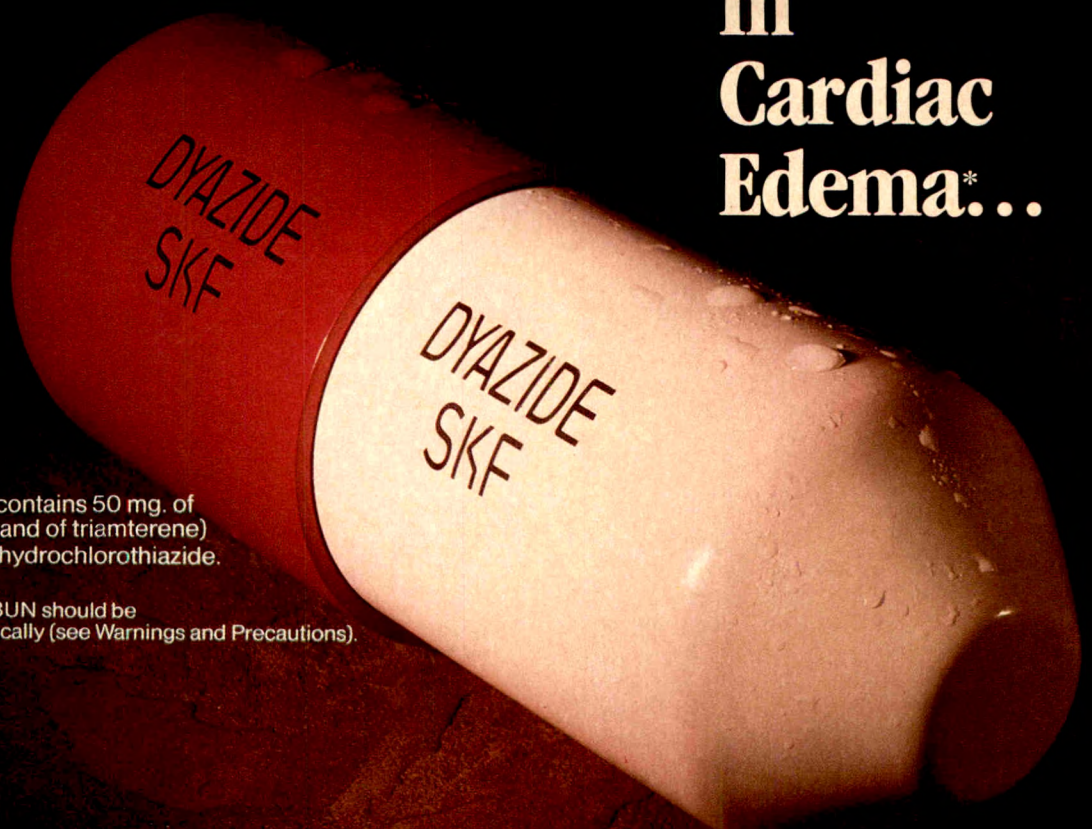

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Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

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WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

(particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both; hyperglycemia and glycosuria (diabetic insulin requirements may be altered); hyperuricemia and gout; digitalis intoxication (in hypokalemia); decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and

measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

Supplied: Dyazide® is supplied in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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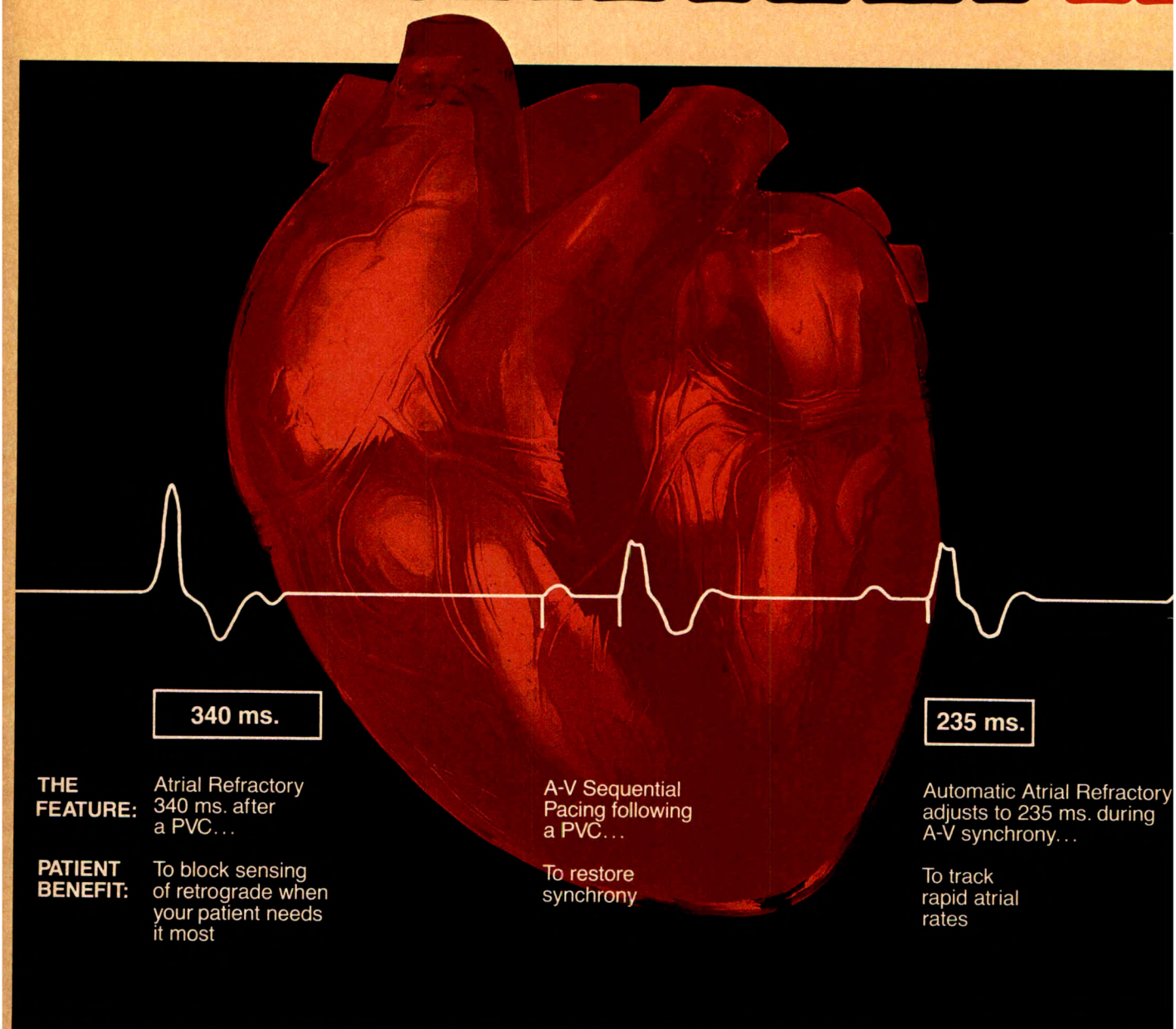

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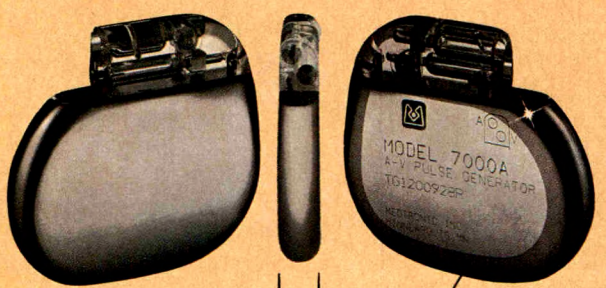

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Intended Use

The Model 7000A universal A-V pulse generator has a wide range of application in patients requiring permanent cardiac pacing where restoration of A-V synchrony and/or sinus modulated rate variability is indicated to improve cardiac output or to protect against arrhythmias related to the sequence of cardiac impulse propagation.

With the Model 7000A programmed in the A-V universal (DDD) mode, indications may include:

- Some of the sick sinus syndrome conditions such as intermittent sinus bradycardia, sinus arrest or SA block.
- Intermittent or complete atrioventricular block with normal sinus activity.
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V interval settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

In the A-V sequential (DVI) mode, the Model 7000A may have application in the following:

- Sick Sinus Syndrome (sinus bradycardia, sinus arrest, SA block, and the brady-tachy syndrome).
- Symptomatic bradycardia.
- Certain drug-resistant and reentrant tachycardias. (Short A-V delay settings may be useful in controlling some reentrant tachycardias.)
- Atrial and ventricular ectopic arrhythmias.

At any time, the Model 7000A can be programmed to the VVI mode in which case the device functions as a ventricular inhibited pulse generator. This mode is intended primarily as a backup mode in situations where it is necessary to disable the atrial circuitry (e.g., atrial lead malfunction).

Contraindications

General: There are no known contraindications to the use of pacing as a therapeutic modality for control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

DDD Mode: The DDD mode is contraindicated in the presence of atrial fibrillation, atrial flutter and rapid atrial rhythms or slow retrograde conduction.

DVI Mode: In the DVI mode, atrial pacing is ineffective in the presence of chronic atrial fibrillation or flutter.

Warnings

Diathermy: Diathermy should not be used on patients with pacemakers because of possible heating effects in the pulse generator and at the implant site.

Electrosurgical Units: Electrosurgical units should never be used in the vicinity of unipolar pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead.

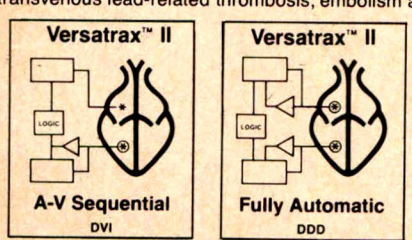
Defibrillation: Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. Positioning a magnet or the programming head over the pulse generator makes it subject to programming. A nominal vertical magnetic field strength of 90 Gauss (in a field measured 1½ inches from the magnet's surface) from a magnet at 1¼ inches from the reed switch is required to initiate asynchronous pacing. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pulse generator. If an electrocautery unit is used, the physician may prefer to program the pacemaker to asynchronous pacing prior to the procedure.

Precautions

The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.



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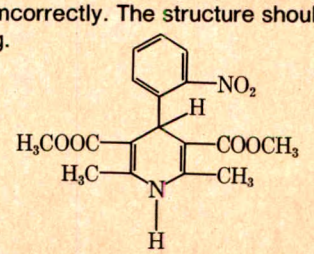
CORRECTION

In the February 18, 1982 issue on page 500 (*Millard RW et al: Differential Cardiovascular Effects of Calcium Channel Blocking Agents: Potential Mechanisms*), the structural formula for nifedipine in Figure 1 presents the ring bonds incorrectly. The structure should show 3 double bonds in the upper ring and 2 in the lower ring.

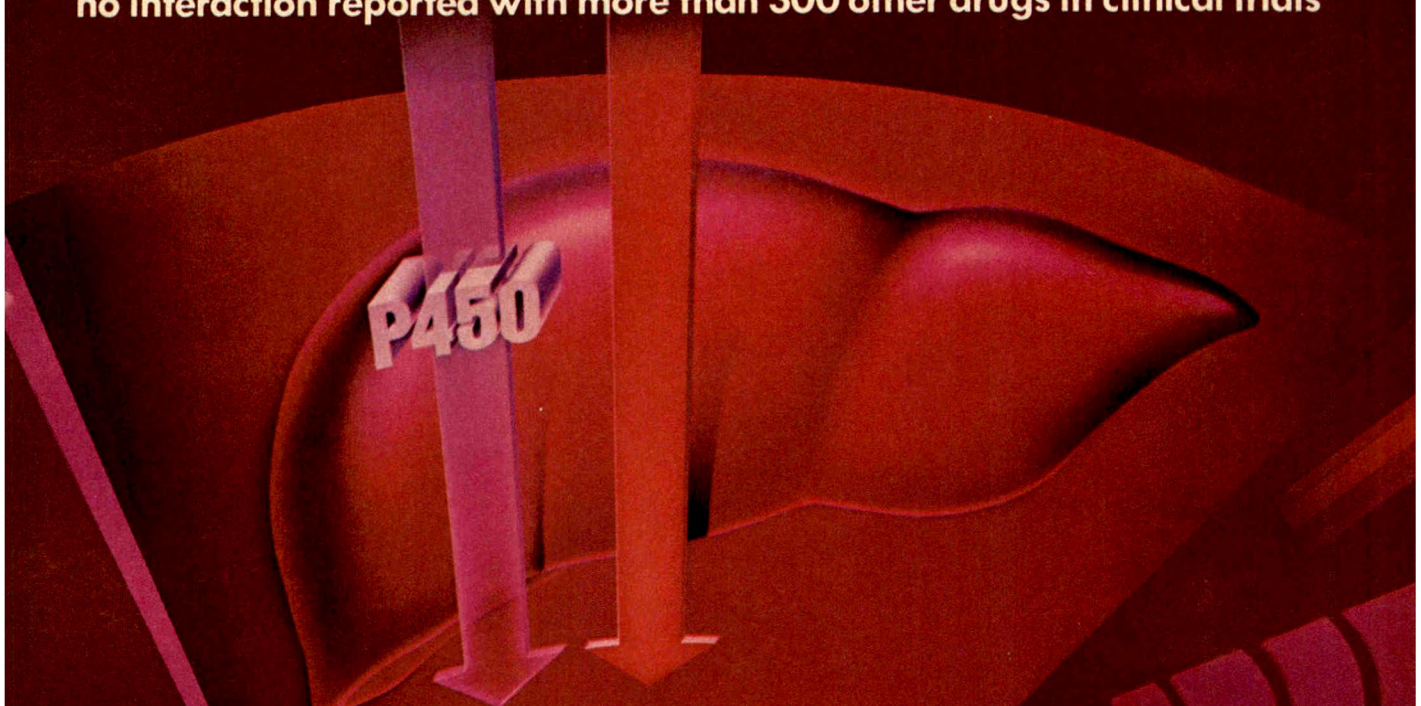


Action without interaction

when given with drugs that utilize the P450 system*

- unlike diazepam and chlordiazepoxide, no interaction with cimetidine
- unlike diazepam, clearance not delayed by oral contraceptives

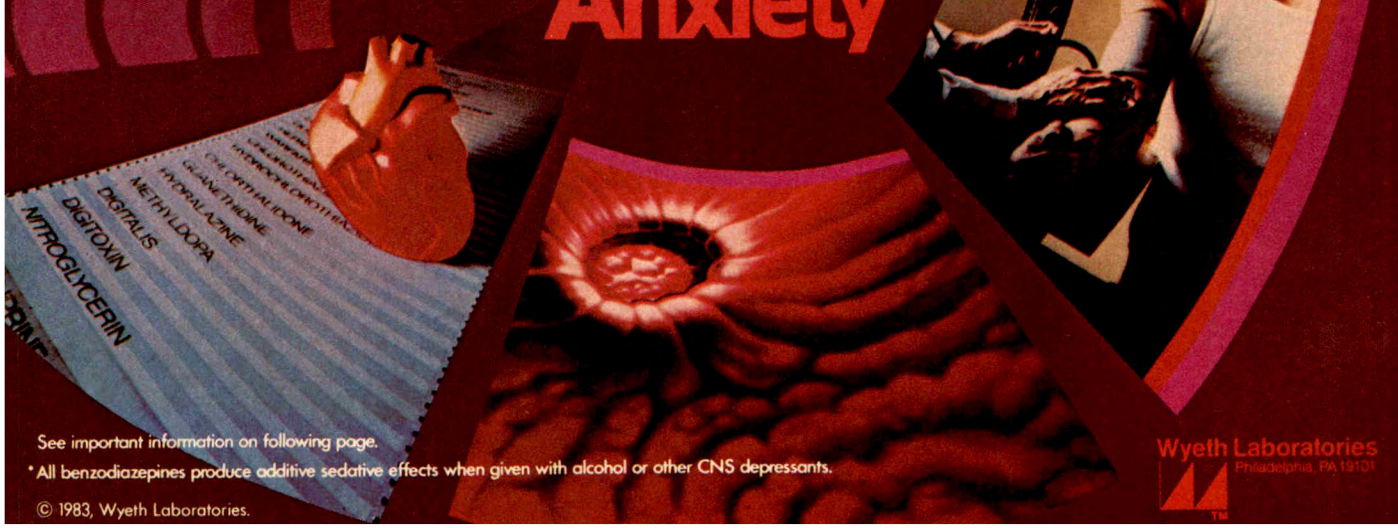
no interaction reported with more than 300 other drugs in clinical trials*



Agent of change

Ativan® (lorazepam)(IV)

for Anxiety



See important information on following page.

*All benzodiazepines produce additive sedative effects when given with alcohol or other CNS depressants.

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NEW TABLET DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) for Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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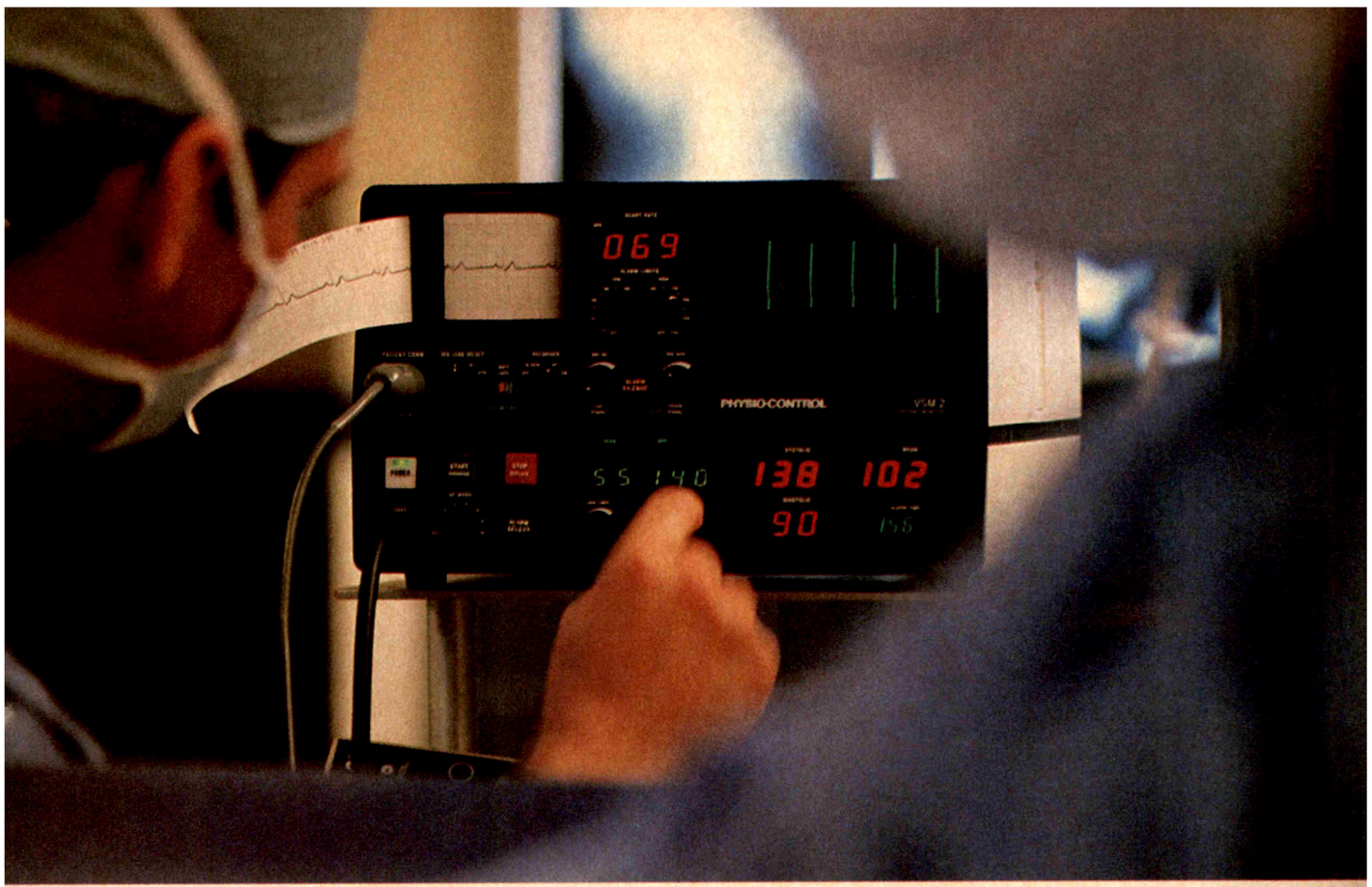

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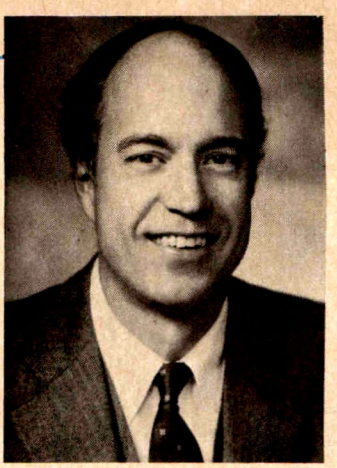
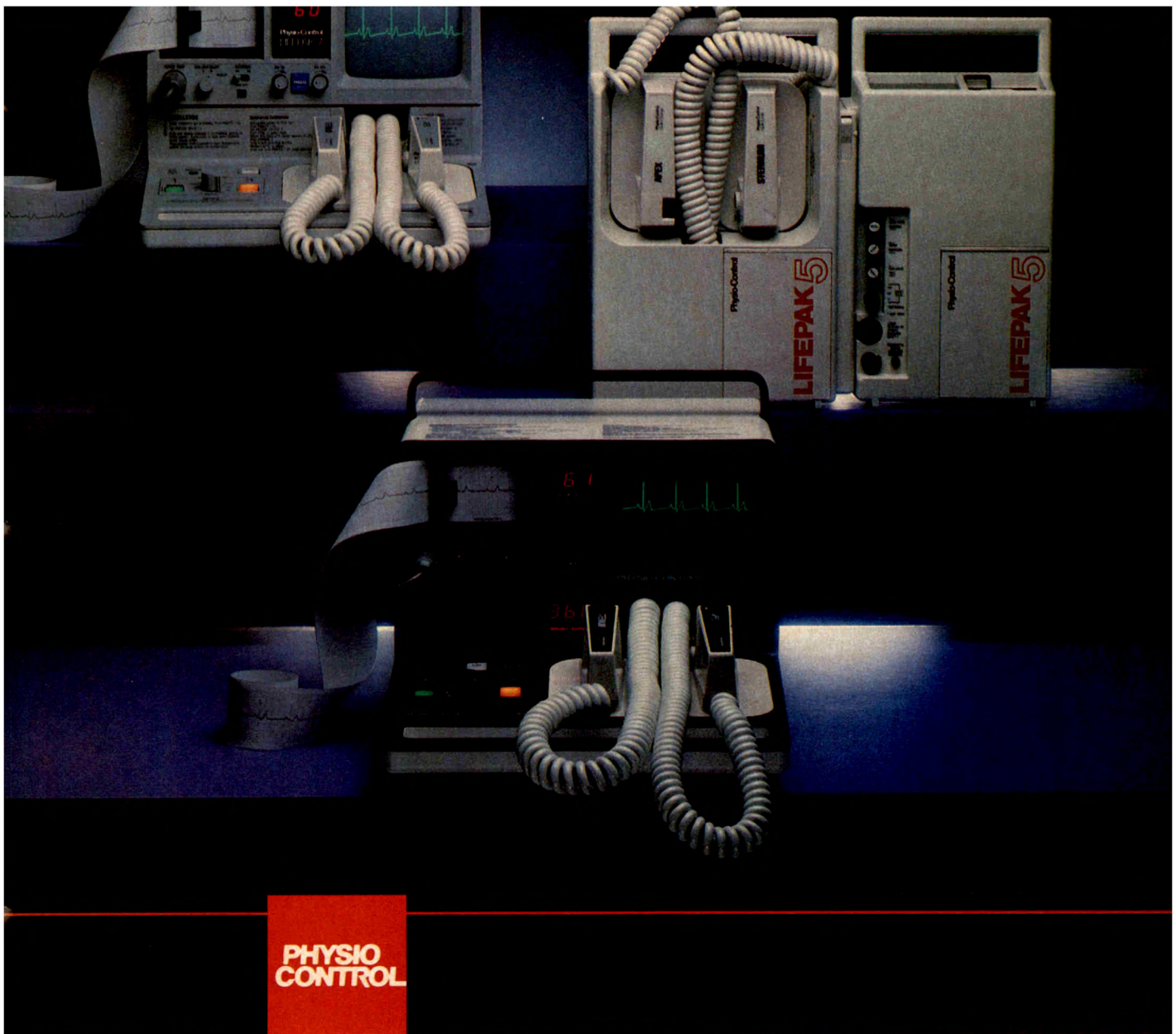


Animal Behavior—Human Behavior—Cardiac Behavior

Considerable study has been made through the years of behavioral characteristics of nonhuman animals—how they communicate, court, mate, fight, care for their young, acquire food, care for their bodies, and so on. Similar studies of humans, of course, are being performed constantly. In contrast to studying general features of one species or another, the pages of this journal focus on how the heart behaves under natural and unnatural conditions, primarily in humans, but in 10% or so of its pages, in nonhuman animals. Our methods of studying the heart change with the changing of our "instruments of precision," our pharmacopia and our ideas, but all the while the heart remains more or less unchanged. Despite the enormous amount of information gained about the heart in the last 75 years, in some respects we have not begun. Our knowledge of the *causes* of cardiac diseases remains poor. Our diagnostic and therapeutic abilities far exceed our knowledge of why the diseases occur in the first place. Despite not knowing precisely why most heart diseases occur, we do know how to prevent many of them. If our total serum cholesterol remains <150 mg/dl, our chances of developing atherosclerosis severe enough to obstruct or aneurysmally dilate an artery are extremely small. If we totally discard salt from the diet, our chances of developing systemic hypertension and all of its consequences, including stroke, are virtually nonexistent. If we live in sanitary, uncrowded and nonpromiscuous environments, our chances of developing rheumatic and syphilitic heart disease are minimal. If alcohol intake is not abused, our chances of developing our most common primary myocardial disease—dilated cardiomyopathy—are relatively small. Thus, most of our present-day common cardiologic conditions are acquired, man-made, of our own doing. The congenital cardiac conditions—holes in cardiac septa, obstructions to flow into or out of a cardiac chamber, improperly connected arteries and veins, malformed valves (bicuspid), which are prone to degenerate (calcific) or to become infected, floppy mitral valves and hypertrophic cardiomyopathy—will remain despite our alterations in dietary and living habits. As we continue to learn more about, and do more for, heart disease, it is humbling to reflect that the heart is only one of the bodies' many organs and that our major subjects of study are only one of the many species on this earth.

William C. Roberts, MD
Editor-in-Chief



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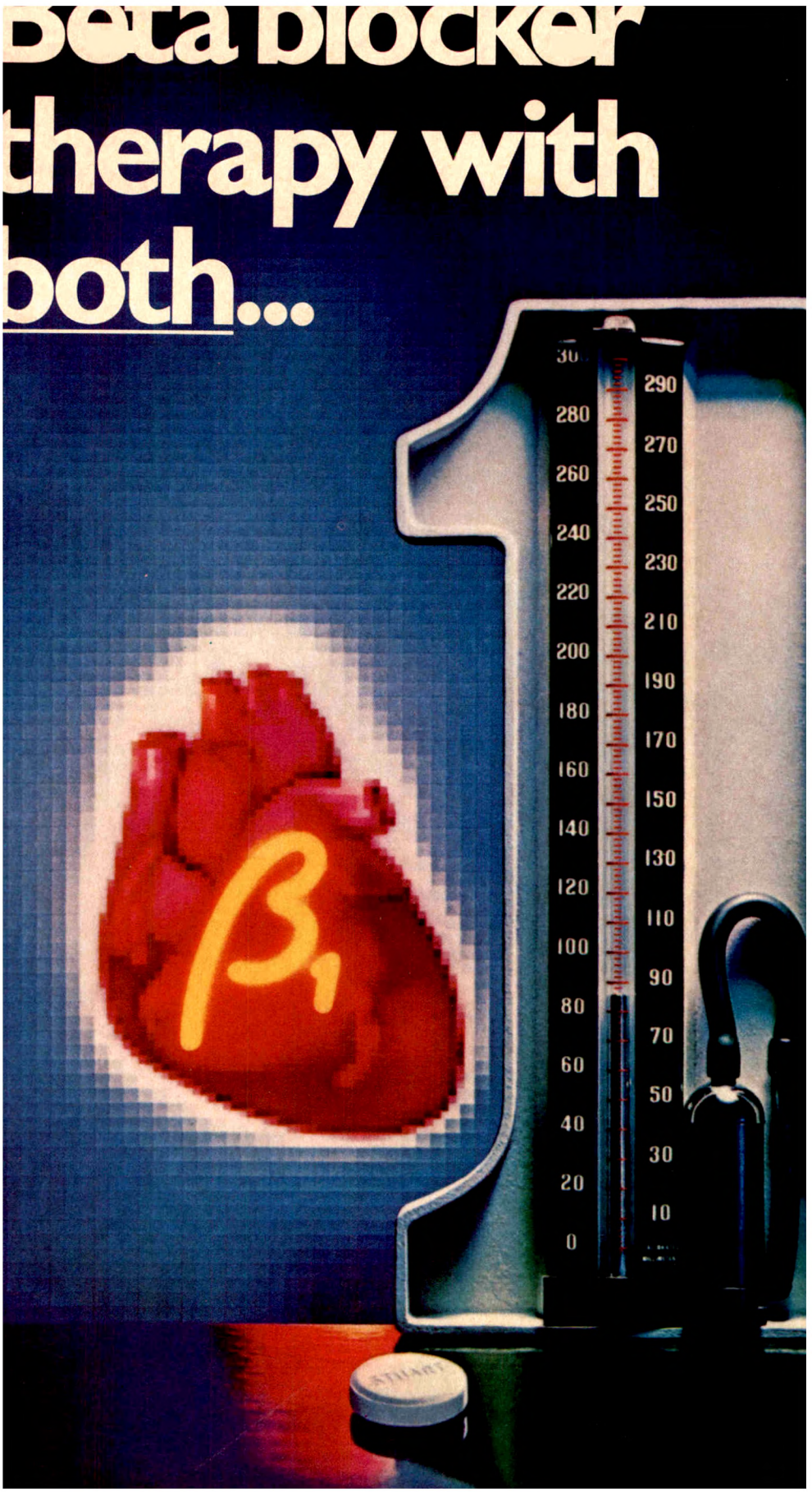
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cardioselectivity*

ONE TABLET

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Tab

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

See last page of this advertisement for brief summary of prescribing information.

ST

TENORMIN® (atenolol)

A beta$_1$-selective blocking agent for hypertension.

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V.).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy.

Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min/1.73 m^2)	Atenolol Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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VOLUME 52

NUMBER 5

CONTENTS

CORONARY HEART DISEASE

431 Effect of Interventions in Salvaging Left Ventricular Function in Acute Myocardial Infarction: A Study of Intracoronary Streptokinase

FLORENCE H. SHEEHAN, DETLEF G. MATHEY, JOACHIM SCHOFER, HANS-JOACHIM KREBBER, and HAROLD T. DODGE

The effect of intracoronary streptokinase on left ventricular (LV) function in acute myocardial infarction (MI) was studied from serial contrast angiograms in 52 patients. Hypokinesia in the MI region improved in 17 of 42 reperfused patients (40%) and in 0 of 10 nonreperfused patients. The ejection fraction did not change in reperfused patients because ejection fraction was normal acutely due to hyperkinesia on the opposite wall and hyperkinesia decreased subsequently, masking the improvement in hypokinesia. Regional LV wall motion must be measured to assess the effect of therapeutic interventions. Early thrombolysis in acute infarction improves LV function.

439 Hemodynamic Effects of Intravenous Prostacyclin in Stable Angina Pectoris

BRIAN G. FIRTH, MICHAEL D. WINNIFORD, WILLIAM B. CAMPBELL, and L. DAVID HILLIS

Prostacyclin (PGI_2) is a naturally occurring vasodilator and inhibitor of platelet aggregation. In this study, the safety and efficacy of incremental doses of intravenously infused PGI_2 were evaluated in patients with coronary artery disease and stable angina pectoris. Ten patients received PGI_2 (maximum dose 10 ng/kg/min) and 7 received placebo. In this dosage, PGI_2 produced flushing but no other adverse effects. It caused an increase in heart rate and cardiac index and a decrease in systemic and pulmonary vascular resistance, without a significant decrease in pulmonary arterial or capillary wedge pressure. There was a concomitant reduction in coronary vascular resistance, which was generally accompanied by an increase in both arterial and venous 6-keto $PGF_{1\alpha}$ concentrations, but no demonstrable change in plasma renin activity.

444 An Improving Prognosis Over Time in Medically Treated Patients With Coronary Artery Disease

DAVID B. PRYOR, FRANK E. HARREL, Jr., KERRY L. LEE, ROBERT M. CALIFF, and ROBERT A. ROSATI

The national mortality rate from coronary heart disease has decreased during the past decade, but the reasons for this decrease are not clear. A decrease in both the mortality rate and total cardiovascular events occurred during the last 10 years in 1,911 medically treated patients with significant coronary artery disease. This decrease cannot be explained by less sick patients being referred for evaluation. This study suggests that at least part of the decrease in coronary heart disease mortality observed nationally is occurring in patients with established coronary disease.

449 Directional ST-Segment Deviation in Graded Exercise Tests Correlated With Motion of the Individual Segments of the Left Ventricular Wall

JAMES N. KARNEGIS, JOHN MATTS, NAIP TUNA, KURT AMPLATZ, RICHARD B. MOORE, HENRY BUCHWALD, and the POSCH Group

The relation of the direction of exercise-induced ST-segment deviation to the specific patterns of motion of the individual segments of the left ventricular (LV) wall was investigated. The first 280 subjects to enter the Program of Surgical Control of Hyperlipidemia (POSCH) were studied by treadmill exercise testing and left ventriculography. All subjects had had 1 previous myocardial infarction and had hyperlipidemia. The results showed that (1) ST-segment elevation with exercise in these subjects is infrequent, (2) exercise-induced ST-segment elevation

Continued on page A23

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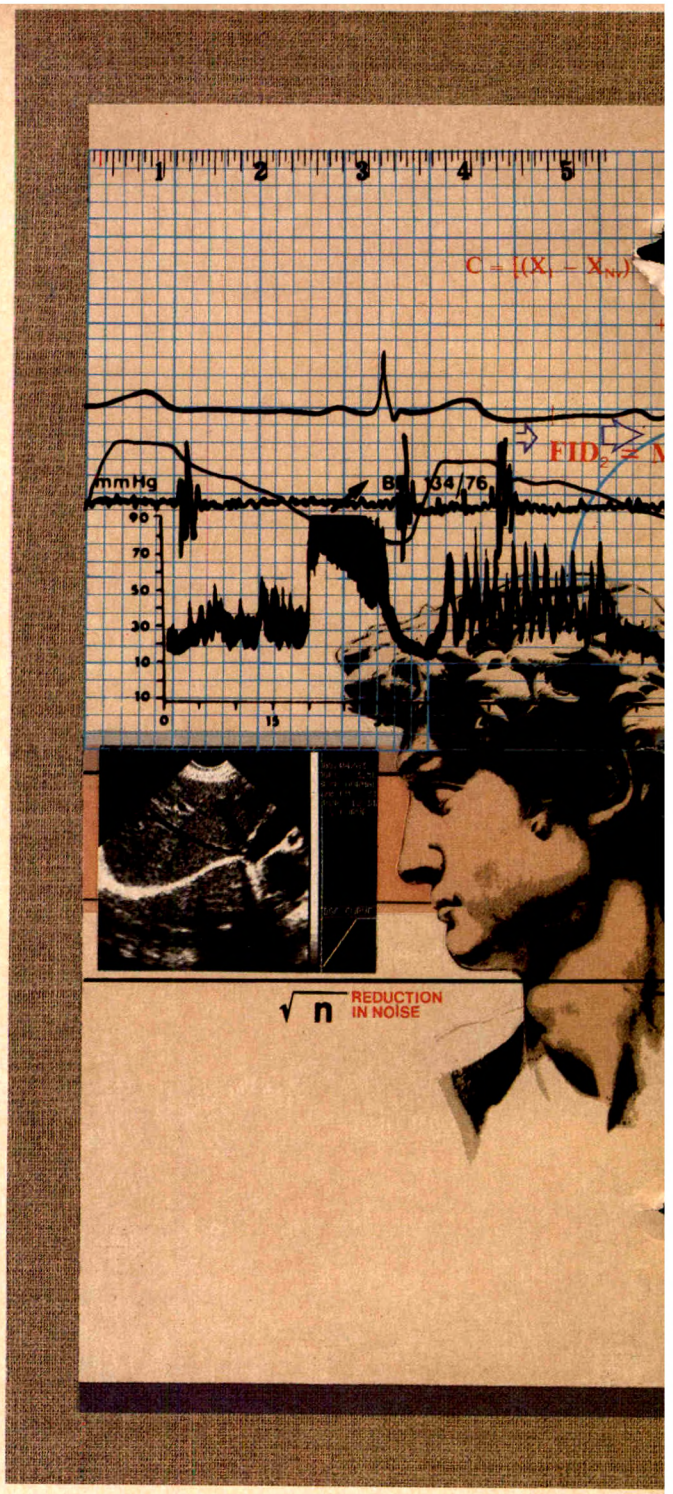

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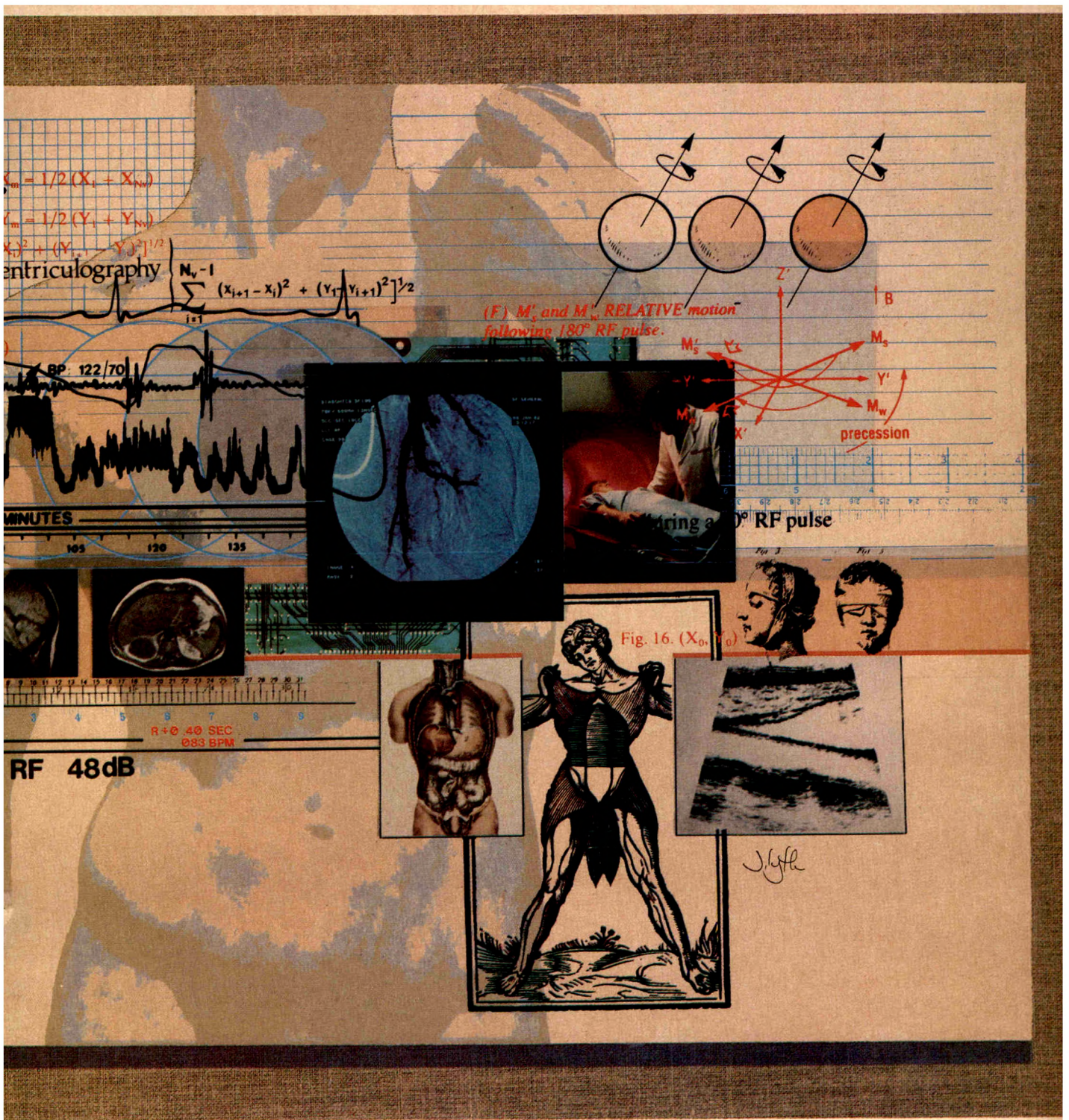

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Indications: Premature atrial and ventricular contractions, aproxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, paroxysmal ventricular tachycardia when not associated with complete heartblock, maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting in extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, light-headedness, and tremor; (3) G.I. symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at the rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G.I. symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 (NDC 0031-6649-63) and 250 (NDC 0031-6649-67) and Dis-co® Unit Dose Packs of 100 (NDC 0031-6649-64).

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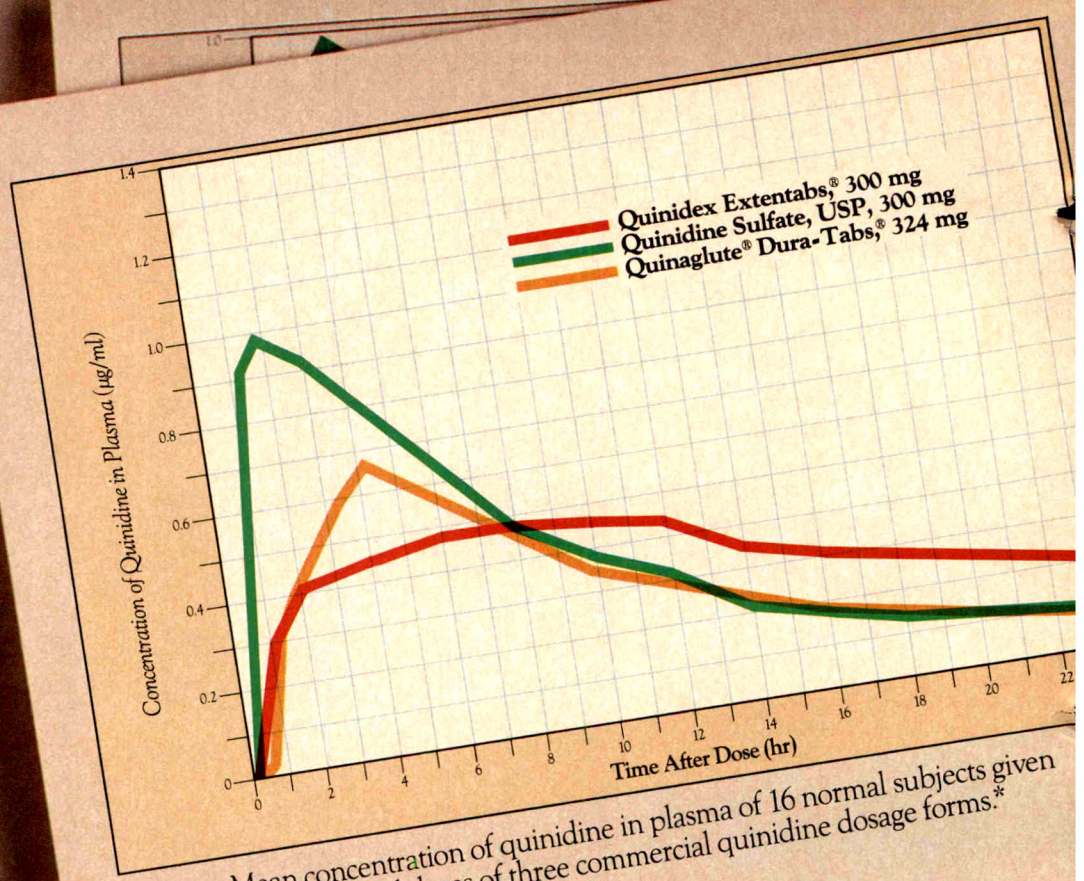

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can occur without evidence in the resting subject of either LV aneurysm or dyskinesia, (3) the group of subjects who had ST-segment elevation with exercise compared with the group in whom ST-segment depression developed had a much greater area of damage to the LV wall, and (4) LV segmental wall motion abnormalities clustered in the inferoposterior area in the group with exercise-induced ST-segment elevation but tended to be scattered throughout the various segments of the LV wall in the group with exercise-induced ST-segment depression.

453 Hemodynamic Effects of Felodipine at Rest and During Exercise in Exertional Angina Pectoris

JEAN-MARIE DETRY, PATRICK M. De COSTER, and JEAN RENKIN

Felodipine, a new calcium antagonist, had a clear antianginal effect in 8 patients whose exercise capacity increased by 20% after oral intake of the drug. The major hemodynamic change observed after felodipine was a decrease in the systemic vascular resistance at rest and during submaximal and maximal exercise. The prevention of angina pectoris was accompanied by significant hemodynamic and electrocardiographic improvements, although the pressure-rate product was unmodified; after felodipine, the maximal pressure-rate product was higher but the electrocardiographic abnormalities were unchanged. These changes in the anginal threshold and in the relation between ST-segment depression and pressure-rate product suggest an improved oxygen delivery to the myocardium.

458 Morphology of Ventricular Premature Beats as an Aid in the Electrocardiographic Diagnosis of Myocardial Infarction

HAROLD DASH and THOMAS J. CIOTOLA

This study of the morphology of ventricular premature beats (VPBs) in the electrocardiographic diagnosis of myocardial infarction (MI) demonstrates that VPBs with a qR pattern are highly specific for MI. Of 760 consecutive patients who underwent cardiac catheterization, 58 had VPBs on the precatheterization electrocardiogram or rhythm strip. Twenty-one of these 58 had MI documented by left ventriculography. The morphology of VPBs had low sensitivity (29%) but high specificity (97%) and predictive value (86%) for the diagnosis of prior MI. VPB analysis complemented the standard electrocardiographic diagnosis of MI in that 2 patients had their MI apparent only on VPB analysis.

462 Prognosis After an Initial Non–Q-Wave Myocardial Infarction Related to Coronary Arterial Anatomy

MICHAEL R. NICHOLSON, GARY S. ROUBIN, LOUIS BERNSTEIN, PHILLIP J. HARRIS, and DAVID T. KELLY

Eighty-six consecutive hospital survivors (aged ≤60 years) of a first non–Q-wave acute myocardial infarction (MI) were followed up prospectively. Coronary arteriography was performed a median of 2 weeks after MI. The size of the MI was small. Forty-nine patients had 1 vessel significantly narrowed by disease (≥70% luminal diameter reduction), and 19 had 2-vessel, 2 had 3-vessel, 3 had left main (≥150% luminal diameter reduction) and 13 had minimal or no coronary artery disease (CAD). Complete occlusion of the MI-related vessel was present in 33 patients. All 33 and an additional 5 patients had collateral vessels to the MI area. During a mean follow-up of 25 months, 1 cardiac death and 4 recurrent infarcts (3 with non–Q-wave MI) occurred. Angina occurred in 53 patients (62%) and responded medically in all but 7, who underwent coronary artery surgery. Angina after MI occurred frequently in patients with severe proximal left anterior descending CAD (≥90%), and in those with CAD (≥50%) in a vessel supplying collaterals to the infarct area. It is concluded that because angina can be managed medically in most patients and the outcome is good, routine coronary angiography is not indicated in asymptomatic survivors (≤60 years) of a first non–Q-wave MI.

466 Effects Induced on Blood Platelets in Ischemic and Nonischemic Myocardium

ERIK THAULOW

Platelet aggregation and retention were reduced in coronary sinus blood compared with superior vena caval blood in 50 patients with coronary artery disease. A reduced platelet responsiveness at rest may reflect refractoriness after mild stimulation. During pacing-induced angina, platelet function remained unchanged in coronary sinus blood in the 27 men who developed net myocardial lactate production, while ADP-induced aggregation, platelet retention and plasma beta-thromboglobulin levels increased in coronary sinus blood in the 23 men without net lactate production. The results suggest that factors other than ischemia activate platelets in the coronary circulation during stress.

Continued on page A27

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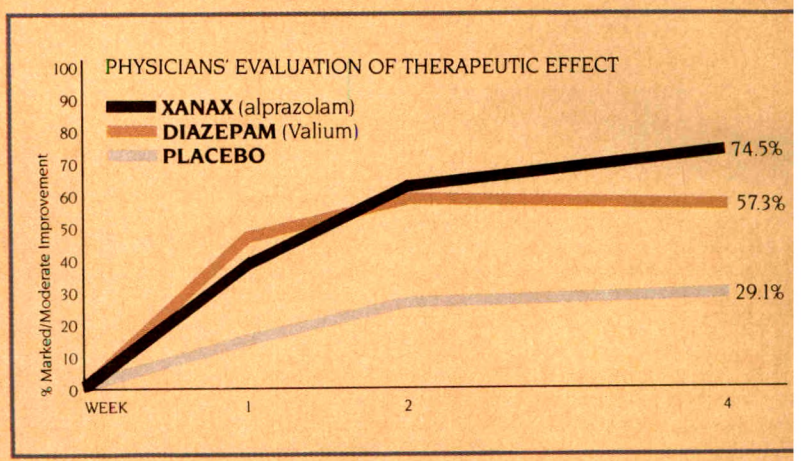

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Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

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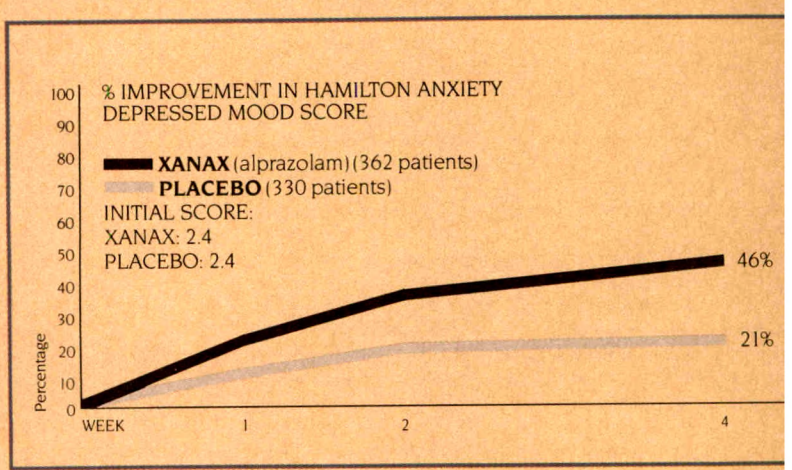

SIMPLE DOSAGE: XANAX 0.25–0.5 mg T.I.D.

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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other Side Effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy, dosage should be tapered. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

BS-1

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 42 (9):347-351, 1981.

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CONTENTS

470 Clinical Data Versus Noninvasive Testing as an Estimate of Coronary Status

SAMUEL H. BROOKS, JOHN W. ALLEN, W. ALLAN EDMISTON, FRANCIS Y. K. LAU, and DAVID H. BLANKENHORN

The step from coronary angiography to surgery is taken primarily on the basis of the ejection fraction (EF) an number of diseased vessels (NV), taken jointly as coronary status (CS). A quantitative definition of CS was estab lished as a principal component of EF and NV. Estimates of EF, NV and CS were made from the clinical data c 60 patients. Correlations with the actual values were EF 87%, NV 93% and CS 93%. When noninvasive dat were added to this model, the correlations increased to EF 95%, NV 99% and CS 98%. When the clinical dat model was applied to 169 patients, the correlations decreased to EF 77%, NV 71% and CS 74%. CS estimate from clinical data alone was set up as a test for angiography for the 169 patients. This test had a sensitivity c 98% and a specificity of 63%. This study demonstrates the feasibility of using clinical data alone in deciding ar giography.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

477 Role of Catheter Lead System for Transvenous Countershock and Pacing During Electrophysiologic Tests: An Assessment of the Usefulness of Catheter Shocks for Terminating Ventricular Tachyarrhythmias

LAWRENCE E. WASPE, SOO G. KIM, JEFFREY A. MATOS, and JOHN D. FISHER

A single intravascular lead system was used for transvenous countershock, programmed stimulation at the ape of the right ventricle, and ventricular pacing during electrophysiologic tests in 13 patients with inducible su tained ventricular tachycardia (VT) or ventricular fibrillation (VF). Leads were left in place for up to 45 days durir serial tests. Synchronized countershock using energies that patients found tolerable (0.01 to 5 joules [J]) term nated 31 of 50 episodes (62%) of induced VT. Episodes of VT cardioverted with these low energies had long cycle lengths than did other episodes. Among 25 matched pairs of VT episodes, pacing methods were just as e fective as low-energy countershock for VT termination. Higher energies (5 to 30 J) were uniformly effective terminating ventricular flutter and VF. There was no evidence of myocardial injury as a result of shocks up to 3 J. However, patients needed increasing sedation when energy exceeded 0.5 J. This catheter system, includi any implantable unit, may be most useful for slightly higher energy conversions (5 to 30 J) of repeated episod of rapid VT or VF, in which pacing techniques are ineffective.

485 Significance of Prolonged Electrocardiographic Pauses in Sinoatrial Disease: Sick Sinus Syndrome

MEIR MAZUZ and HOWARD S. FRIEDMAN

Eighty-four patients (2.5%) were found to have prolonged (≥2.0 seconds) sinoatrial pauses in a review of Holt recordings. No relation was found between average length of pauses, presence of symptoms or risk of deat Patients who received a pacemaker were older and more likely to be male and to have symptoms. Pacemak recipients were not different from nonrecipients with respect to average longest pause, mechanism of paus underlying heat condition or average time of followup. The survival rate was not improved by permanent pac maker implantation. Thirteen patients who had syncope did not receive a pacemaker; 2 of them had noncardi deaths and none had a subsequent syncopal episode. Ten patients with syncope received a pacemaker; 3 die and 3 survivors continued to complain of dizziness. Of the 37 patients who were asymptomatic at the time of r cording, only 1 patient subsequently had a syncopal episode. Thus, length of sinoatrial pauses correlates poo with symptoms and does not predict sudden death.

490 Cardiac Arrhythmia and Conduction Disturbances During Sleep in 400 Patients With Sleep Apnea Syndrome

CHRISTIAN GUILLEMINAULT, STUART J. CONNOLLY, and ROGER A. WINKLE

Four hundred patients with sleep apnea had a 24-hour Holter electrocardiogram and a polysomnogram dur the late afternoon and nocturnal sleep. Cardiac arrhythmias or abnormalities of conduction were observed in 1 patients. The mean number of apneic events, age, weight and lowest oxygen saturation were not significant fa tors in differentiating the 193 patients from the other 207 patients. Eight patients had unsustained ventricu tachycardia, 43 had sinus arrest that lasted 2.5 to 13 seconds, 31 had second-degree atrioventricular conduct block and 75 had frequent premature ventricular contractions (>2/min). Fifty patients with significant arrhy mias had no arrhythmias after tracheostomy except for premature ventricular contractions.

Continued on page A31

in cardiovascular therapy

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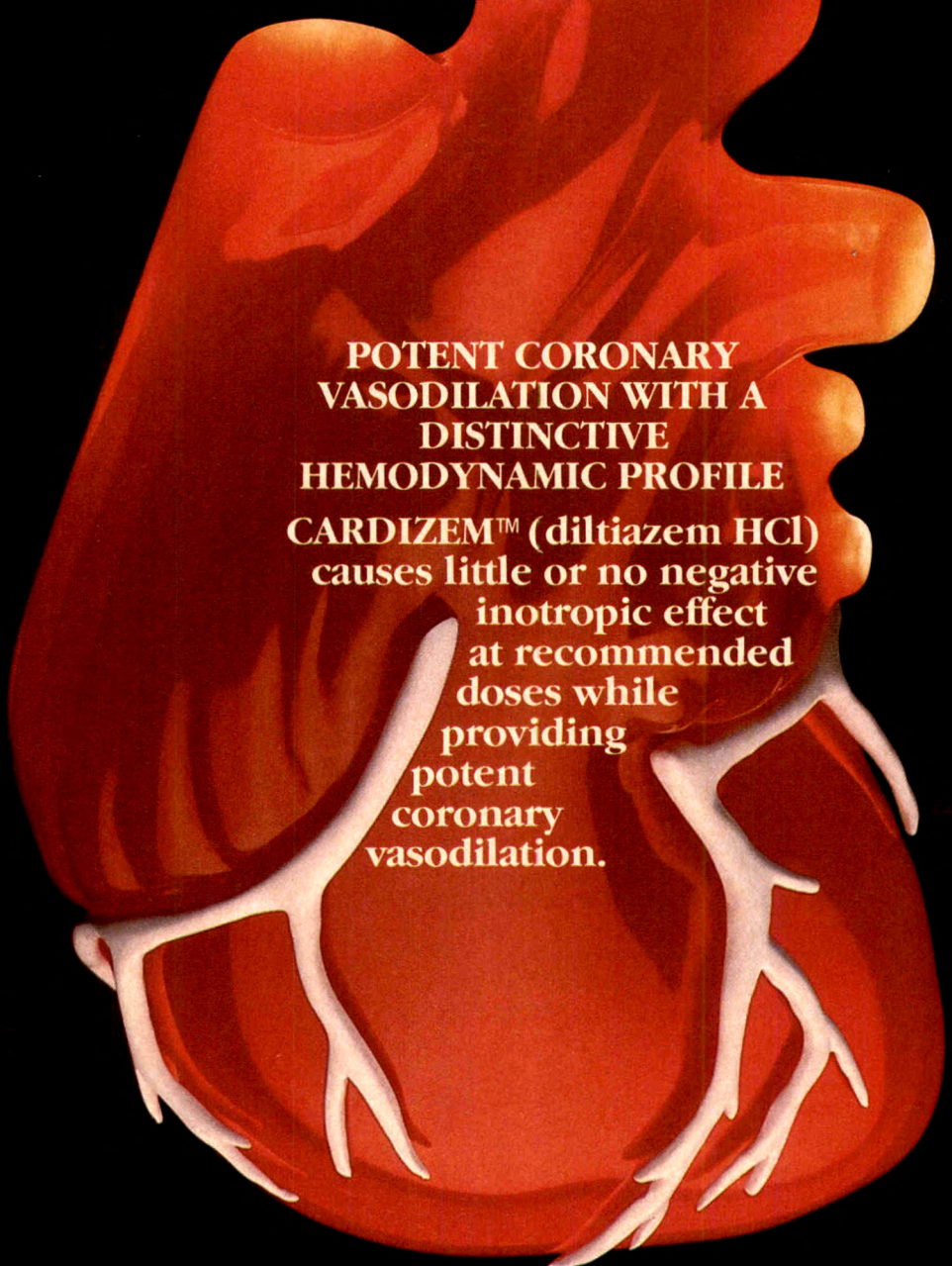
from
Marion Laboratories



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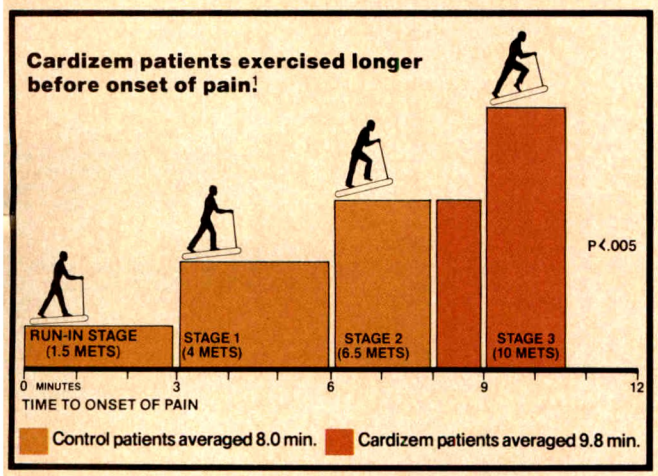
INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY* WITH A LOW INCIDENCE OF SIDE EFFECTS

Calcium channel blockade with CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

CARDIZEM™ (diltiazem HCl) ALLOWS PATIENTS TO SIGNIFICANTLY PROLONG EXERCISE TOLERANCE, EVEN IN DEMANDING BRUCE PROTOCOL EXERCISE TESTS[1] (n = 15)†



This study is of special significance because patients not only exercised longer but *to the next higher stage* in the Bruce protocol.

A Bruce protocol with a run-in stage was used for all tests. Each stage lasts three minutes.

In other studies, Cardizem produced 41% to 68% reduction of Prinzmetal's variant angina attacks.[2]

Therapy with Cardizem produced a low incidence of side effects.

In placebo-controlled trials conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with Cardizem have been:

- Nausea 2.7%
- Swelling/edema 2.4%
- Arrhythmia 2.0%
- Headache 2.0%
- Rash 1.8%
- Fatigue 1.1%

Other reactions reported infrequently (less than 1%) are listed in full prescribing information on adjacent page.

†This study is a report from one center in a multicenter study.

References:

1. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl):234-238, 1980.
2. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.

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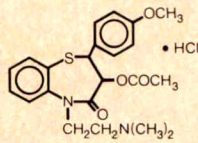
Please see adjacent page for full prescribing information.

PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (four of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem tid of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to the drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

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3/83

CONTENTS

495 Encainide for Refractory Ventricular Tachyarrhythmia

BRIAN CHESNIE, PHILIP PODRID, BERNARD LOWN, and ERNEST RAEDER

Encainide was studied in 80 patients with a history of malignant ventricular arrhythmia. On the basis of the frequency of arrhythmia, efficacy was judged noninvasively with monitoring and exercise testing in 63 patients and with invasive electrophysiologic testing in 17 patients. Overall, encainide was effective in 34 patients (54%) evaluated noninvasively and in 7 patients (44%) who had electrophysiologic testing. Daily dose and blood levels were equivalent in responders and nonresponders. Toxic side effects occurred in 24 patients (30%), 18 of whom had an aggravation of arrhythmia. Increase in arrhythmia correlated with larger doses and blood levels of the drug. After an average of 21 months, 23 patients continue taking the drug and are free of arrhythmia and adverse effects.

501 Induction of Clinical Ventricular Tachycardia Using Programmed Stimulation: Value of Third and Fourth Extrastimuli

DAVID E. MANN, JERRY C. LUCK, JERRY C. GRIFFIN, JOHN M. HERRE, MARIAN C. LIMACHER, SHARON A. MAGRO, NANCY W. ROBERTSON, and CHRISTOPHER R. C. WYNDHAM

Initiation of ventricular tachycardia (VT) in the electrophysiology laboratory was analyzed in 142 patients who received up to 4 extrastimuli and ventricular burst pacing in the right ventricle. Fifty-three patients had previously documented spontaneous episodes of VT or ventricular fibrillation and 68 patients had no history of VT. Twenty-one patients with a history of sudden death but without documented arrhythmia were excluded from further analysis. In patients with sustained VT, use of third and fourth extrastimuli increased the yield of inducible clinical VT from 37 to 65% compared with use of first and second extrastimuli alone. Clinical VT was not inducible in 10 patients with spontaneous nonsustained VT. Use of third and fourth extrastimuli caused increased induction of nonclinical forms of VT, usually polymorphic and nonsustained, in both patient groups. We conclude that use of third and fourth extrastimuli in the right ventricle improves the yield of inducible clinical VT, but at a cost of increased induction of nonclinical varieties of VT.

507 Hemodynamic Effects of Encainide in Patients With Ventricular Arrhythmia and Poor Ventricular Function

MAGDI H. SAMI, VILMA A. DERBEKYAN, and ROBERT LISBONA

To evaluate the hemodynamic effects of encainide, 19 patients with complex ventricular arrhythmias and poor left ventriclar function (ejection fraction [EF] <45%) underwent gated cardiac scanning before and during steady-state oral encainide therapy. Sixty-three percent had congestive heart failure before they received encainide. Gated scanning was performed 3 days after discontinuing all antiarrhythmic drugs, and was repeated 1 to 2 weeks later on a dose of encainide that was found effective in reducing the frequency of ventricular premature beats by 80% on a 24-hour Holter recording. EFs before and during encainide averaged 22 ± 10% (± standard deviation) and 25 ± 14%, respectively (difference not significant). None of the patients had a decrease in EF of >5% or worsening of congestive heart failure. Other hemodynamic measurements also remained unchanged. Digoxin blood levels measured in 10 patients remained stable during encainide therapy.

CONGESTIVE HEART FAILURE

512 Circulatory Autoregulation in Chronic Congestive Heart Failure: Responses to Head-Up Tilt in 41 Patients

SPENCER H. KUBO and ROBERT J. CODY

To evaluate mechanisms that regulate the response to postural change in patients with chronic congestive heart failure, the hemodynamic and vasoactive hormonal responses to head-up tilt in 41 patients were examined. Peripheral venous pooling was present in only 18 patients and was inversely correlated with baseline pulmonary wedge pressure. Baseline supine hemodynamic indexes of these 18 patients indicated less severe heart failure than in the 23 patients who did not demonstrate venous pooling. Overall, 3 patterns could be identified. Of the 18 patients with venous pooling, 12 maintained many of the elements of normal postural response, with increases in systemic vascular resistance and circulating norepinephrine that maintain blood pressure constant. Six patients did not increase resistance in response to peripheral venous pooling and had major decreases in blood pressure similar to idiopathic orthostatic hypotension. The larger group of 23 patients with more severe failure did not have peripheral venous pooling and, hence, no afferent stimulus for reflex changes. Thus, the hemodynamic and neurohormonal responses to head-up tilt in heart failure are heterogeneous and may be influenced by severity of disease.

Continued on page A34

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AVIUS is reliable.
Its circuitry is based on time-proven Intermedics circuitry. And it has the largest battery capacity of any available DVI pacemaker.

AVIUS restores A-V synchrony **thus increasing cardiac output because it is a dual chamber pacing system.**

AVIUS practically eliminates pacemaker syndrome.

AVIUS. The pacemaker you can count on for hassle free pacing.
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INDICATIONS FOR USE: Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, and heart block unresponsive to drug therapy.

A-V sequential pacing is specifically indicated for treatment of conduction disorders that require restoration of both rate and atrio-ventricular synchrony. A-V sequential pacing may also be indicated for patients with extensive myocardial infarction with A-V block and sinus bradycardia.

CONTRAINDICATIONS AND SIDE EFFECTS: There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

PRECAUTIONS: See the "Cautionary notes" section of the Physicians Manual for the Intermedics cardiac pluse generator to be implanted. Discussion includes Possible Complications, Environmental Hazards (electrocautery, diathermy, defibrillation, therapeutic radiation, home appliances, and industrial and special environments), and Effects of Drugs.

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CONTENTS

VAVULAR HEART DISEASE

519 Accuracy of Evaluation of the Presence and Severity of Aortic and Mitral Regurgitation by Contrast 2-Dimensional Echocardiography

CHERYL L. REID, DAVID T. KAWANISHI, CHARLES R. McKAY, URI ELKAYAM, SHAHBUDIN H. RAHIMTOOLA, and P. ANTHONY N. CHANDRARATNA

Contrast 2-dimensional (2-D) echocardiography was performed during cardiac catheterization to compare the technique with cineangiography in evaluating the presence and severity of aortic (AR) and mitral regurgitation (MR). A physiologic solution was injected through the intracardiac catheter while echocardiographic recordings were obtained in multiple views. AR was evaluated in 35 patients; sensitivity, specificity and predictive accuracy was 100% for detection of AR by 2-D echocardiography. Severity of AR based on visual assessment by both 2-D echocardiography and cineangiography correlated with $r = 0.998$. MR was evaluated in 59 patients. Sensitivity for detection of MR by 2-D echocardiography was 84% and specificity 89%. Severity of MR by both methods correlated with $r = 0.998$. Contrast 2-D echocardiography for the evaluation of the presence and severity of AR and MR is both sensitive and specific. Use of 2-D echocardiography in the cardiac catheterization laboratory should be of greatest value when the use of cineangiography is limited by the dose of contrast medium, radiation or technical problems.

525 Two-Dimensional Echocardiographic Determination of Right Atrial Emptying Volume: A Noninvasive Index of Quantifying the Degree of Tricuspid Regurgitation

NICHOLAS L. DePACE, JIAN-FANG REN, MORRIS N. KOTLER, GARY S. MINTZ, DEMETRIOS KIMBIRIS, and PETER KALMAN

Using a computerized light-pen method to trace the right atrial (RA) border during systole and diastole in the apical 4-chamber view, single-plane volume determinations were calculated in 10 normal subjects (Group I), 18 patients with atrial fibrillation (AF) and no tricuspid regurgitation (TR) (Group II), 14 patients with mitral stenosis and mild TR (Group IIIa), and 8 patients with mitral stenosis and severe TR (Group IIIb). TR was quantitated as absent, mild or severe by contrast right ventriculography. The mean RA emptying volume, which equals RA end-systolic volume − RA end-diastolic volume, was 15 ± 5.0 for Group I, 18 ± 3.0 for Group II, 30 ± 8.0 for Group IIIa and 72 ± 25 for Group IIIb. All 8 patients with severe TR had an RA emptying volume >40 ml, compared with none of the 14 patients with mild TR ($p < 0.001$). Thus, in patients with mitral stenosis, RA emptying volume is useful in separating severe TR from mild TR.

530 Influence of Volume Loading on Intraoperative Hemodynamics and Perioperative Fluid Retention in Patients With Valvular Regurgitation Undergoing Prosthetic Replacement

J. GILBERT STONE, PAUL F. HOAR, and HOSHANG J. KHAMBATTA

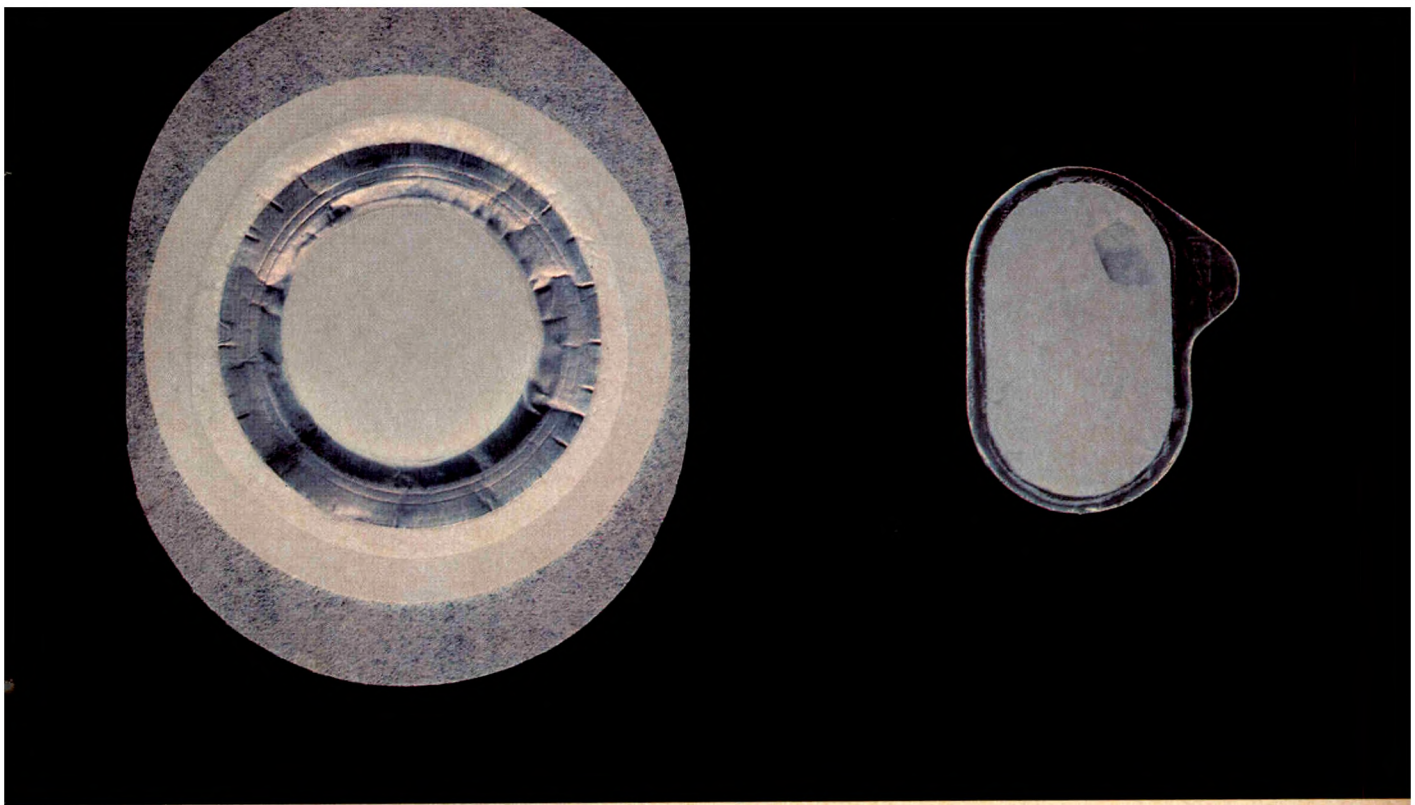
Preload and afterload were controlled intraoperatively in 2 groups of patients with valvular regurgitation and congestive heart failure to determine the effect of fluid loading on weight gain and subsequent recovery. Sixteen patients were given 1 liter of crystalloid with nitroprusside infused at 1 μg/kg/min and 16 received 4 liters of crystalloid with nitroprusside at 4 μg/kg/min. Arterial and filling pressures were kept the same in both groups. Heart rate and vascular resistance became significantly lower and cardiac index and stroke volume significantly higher in the fluid-augmented group. The transition to cardiopulmonary bypass was smoother for the fluid-augmented patients. Mean weight gain at surgery was equal in the 2 groups (3 kg). For the first 2 postoperative days, body weight remained unchanged, and thereafter, both groups lost weight at a rate of 0.6 kg/day. Thus, a modest amount of operative weight gain in these patients is inevitable, benign and independent of the volume of prebypass infused fluid.

534 Mitral Valve Prolapse Syndrome: Analysis of 62 Patients Aged 60 Years and Older

ALBERT J. KOLIBASH, CHARLES A. BUSH, MARY BETH FONTANA, JOSEPH M. RYAN, JAMES KILMAN, and CHARLES F. WOOLEY

Sixty-two patients 60 to 81 years of age were diagnosed as having mitral valve prolapse on the basis of classic auscultatory, echocardiographic and angiographic findings. These patients presented in a clinically predictable pattern with symptoms of disabling chest pain, arrhythmias and the presence of a murmur of mitral regurgitation with congestive heart failure. Twenty patients presented with disabling chest pain, 7 of whom had significant coronary artery disease. The presence of coronary artery disease could not be detected on the basis of history or noninvasive laboratory studies alone. Sixteen patients with palpitations had a broad spectrum of rhythm disor-

Continued on page A38



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Transdermal Infusion System

DESCRIPTION: The Nitro-Dur Transdermal Infusion System contains nitroglycerin in a gel-like matrix composed of glycerin, water (purified), lactose, polyvinyl alcohol, povidone and sodium citrate to provide a continuous source of the active ingredient. Nitro-Dur is available in dosage sizes 5cm², 10cm², 15cm² and 20cm², containing 26 mg, 51 mg, 77 mg and 104 mg of nitroglycerin, respectively, thereby providing a range of dosing levels of nitroglycerin. Nitro-Dur has a rated release in vivo of approximately 0.5mg/cm²/24 hours. Each unit is sealed in a polyester-foil-polyethylene laminate. The bandage portion consists of a medical grade non-woven, heat sealable, microporous tape.

CLINICAL PHARMACOLOGY: When the Nitro-Dur system is applied to the skin, nitroglycerin is absorbed continuously through the skin into the systemic circulation. This results in active drug reaching the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth muscle relaxant with vascular effects manifested predominantly by venous dilation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption secondary to vascular smooth muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been an increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.

In bioavailability studies using healthy volunteers,[1] transdermal absorption of nitroglycerin from Nitro-Dur achieved steady state venous plasma levels comparable to that of sublingual nitroglycerin and maintained these levels for 24 hours. Detectable plasma levels were attained within 30 minutes after application of the unit, and were still detectable 30 minutes after removal of the unit.

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS: The Nitro-Dur system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of angina patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

Nitro-Dur is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing Nitro-Dur therapy. If headache persists, the Nitro-Dur dosage should be reduced.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the Nitro-Dur dosage should be reduced or use of the product discontinued.

HOW SUPPLIED: Nitro-Dur Transdermal Infusion System, 5cm², 10cm², 15cm² and 20cm², is available in unit dose packages of 28 and hospital packs of 100.

CAUTION: Federal law prohibits dispensing without prescription.

PATIENT INSTRUCTIONS FOR APPLICATION: Patient instructions are furnished with each unit dose package.

For complete prescribing information, please see package insert.

[1]Data on file: Key Pharmaceuticals, Inc. 07/83

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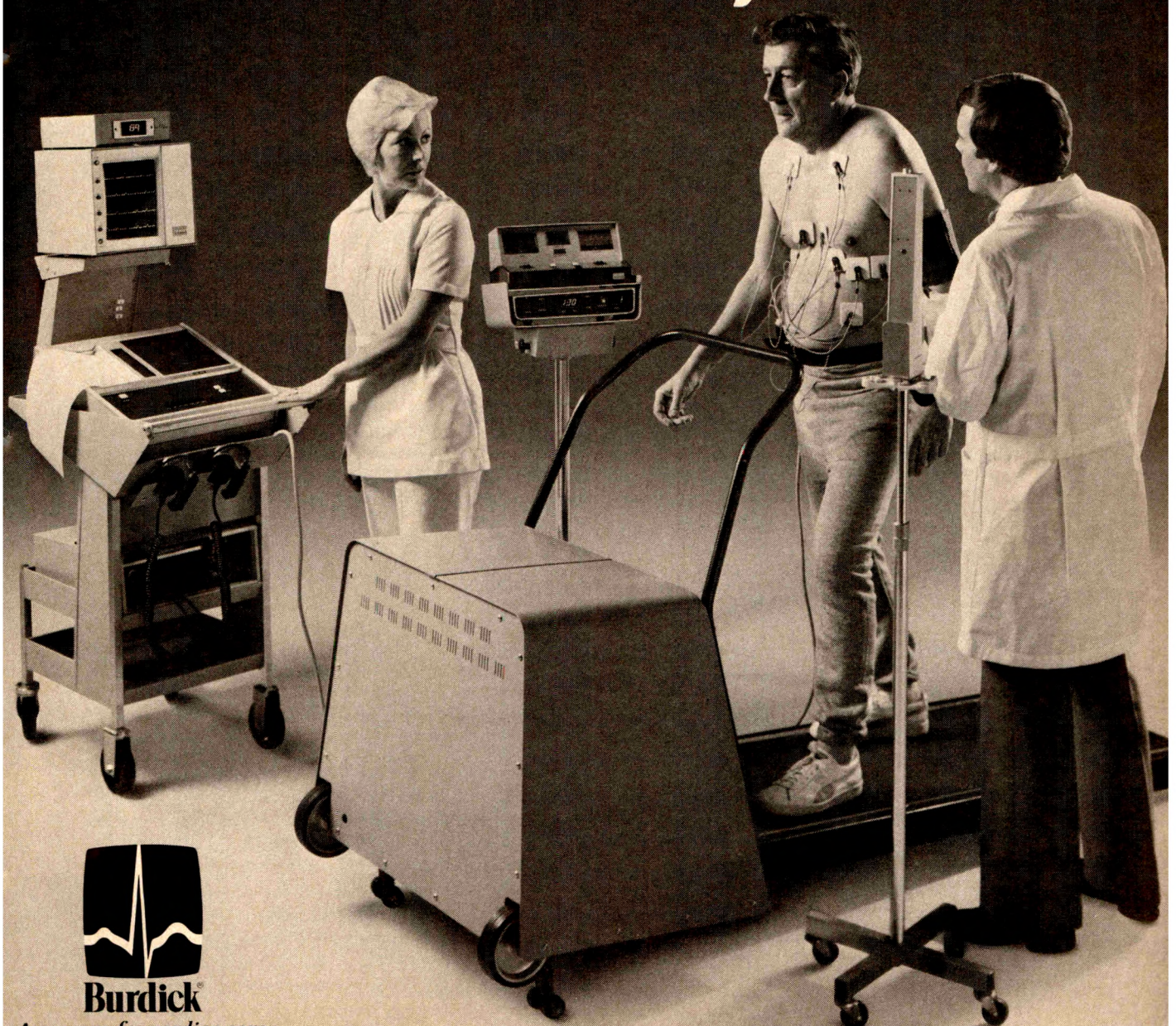

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ders, including supraventricular and ventricular arrhythmias. Two patients in this group had prehospital sudden death and 2 others had evidence of systemic embolization. Twenty-six patients presented with mitral regurgitation and congestive heart failure, 21 of whom required mitral valve surgery and were found to have enlarged, floppy mitral valves with redundant leaflets at the time of surgery. Histologic examination showed extensive myxomatous changes throughout the valve leaflets. Thus, mitral valve prolapse was identified in this elderly group of patients who presented with clinical findings similar to those seen in the younger population with mitral valve prolapse.

540 Valve of Isometric Exercise Testing During Cardiac Catheterization in Mitral Stenosis

HEIKKI V. HUIKURI and JUHA T. TAKKUNEN

The isometric handgrip exercise test was performed during preoperative diagnostic catheterization by 28 patients with mitral stenosis (MS). Eighteen patients who underwent mitral valve surgery were recatheterized and reevaluated clinically 12 months after surgery. Sixteen patients whose mitral valve pressure gradient increased >4 mm Hg during isometric exercise had an increase in peak systolic pressure/end-systolic volume ratio ($p < 0.001$) and their ejection fraction remained unchanged (group A). Twelve patients whose mitral valve pressure gradient decreased or increased <4 mm Hg had a decrease in ejection fraction ($p < 0.001$), and their peak systolic pressure/end-systolic volume ratio remained unchanged during exercise (group B). In the total group, a correlation existed between the change in mitral pressure gradient and the changes in measures of left ventricular (LV) function during exercise. The patients in group A had a significant improvement in symptoms and exercise tolerance after surgery and the patients in group B had only minimal symptomatic improvement and their exercise tolerance did not improve after surgery. Thus, the change in mitral valve pressure gradient during isometric exercise appears to reflect the LV response to exercise.

CARDIOMYOPATHY

544 Influence of Verapamil Therapy on Left Ventricular Performance at Rest and During Exercise in Hypertrophic Cardiomyopathy

PETER HANRATH, MICHAEL SCHLÜTER, FRANK SONNTAG, JÖRG DIEMERT, and WALTER BLEIFELD

The effects of chronic high-dose verapamil treatment on resting and exercise hemodynamics in patients with hypertrophic cardiomyopathy are presented. Systolic cardiac performance in terms of stroke volume index improved significantly in these patients at rest as well as during maximal symptom-limited exercise. The main factors responsible for this improvement are believed to be the vasodilative effect of verapamil and the reduction in heart rate. Verapamil-induced improvement of diastolic cardiac performance is shown by a significant decrease of end-diastolic pulmonary artery pressure during exercise.

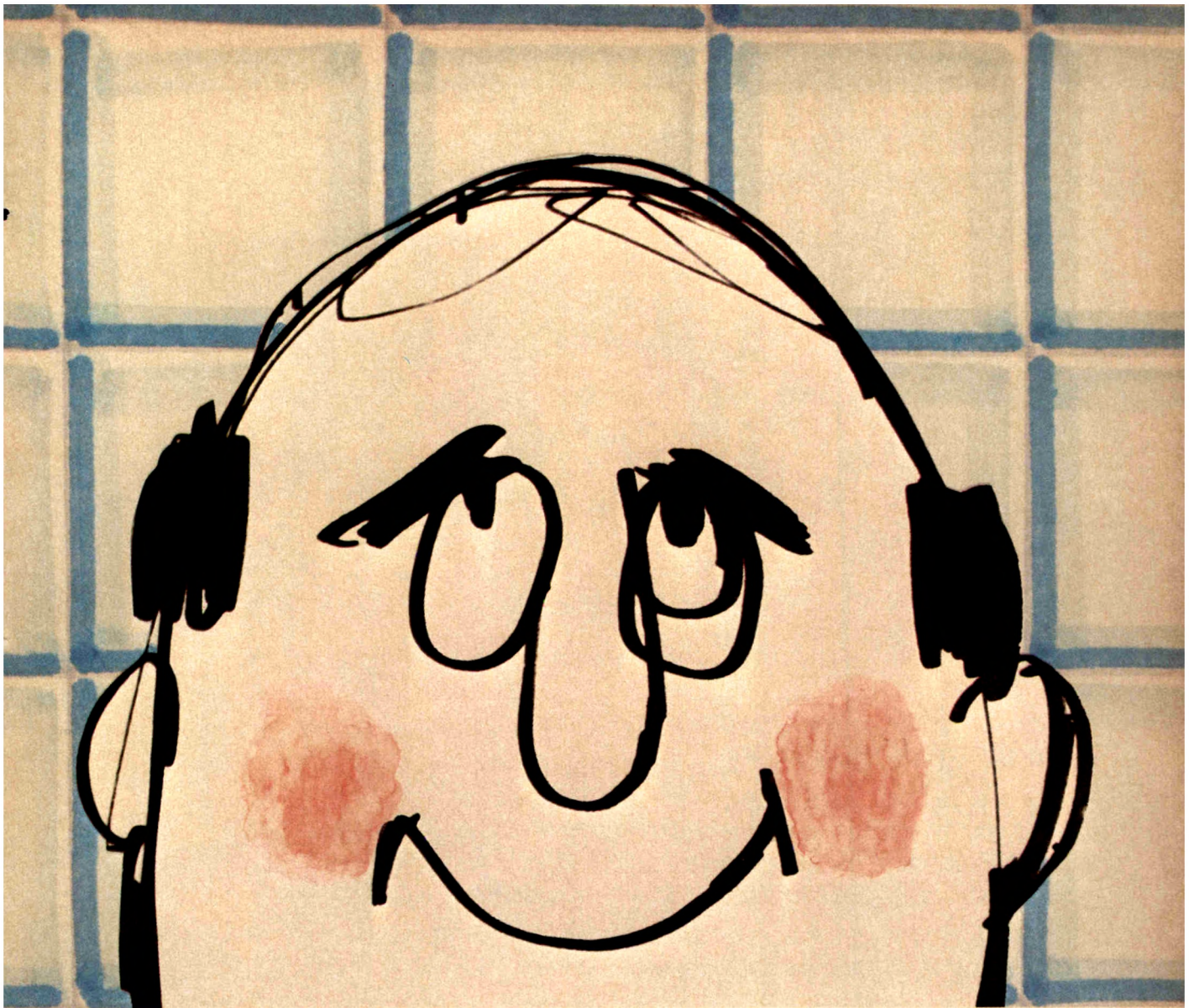
CONGENITAL HEART DISEASE

549 Changing Results and Concepts in the Surgical Treatment of Double-Outlet Right Ventricle: Analysis of 137 Operations in 126 Patients

GIAN PICCOLI, ALBERT D. PACIFICO, JOHN W. KIRKLIN, EUGENE H. BLACKSTONE, JAMES K. KIRKLIN, and LIONEL M. BARGERON, Jr.

One hundred thirty-seven operations (98 repairs, 23 preliminary operations and 16 palliative operations for uncorrectable malformations) were performed for double-outlet right ventricle (DORV) from January 1967 through July 1982, with 36 hospital deaths (26%). Incremental risk factors for death after 42 "classic" DORV repairs included young age, type of repair and era. In the current era (1978 through July 1982), 1 of 19 (5%) died (70% confidence limits 0.7 to 17%), with the risk of young age evident only under age 3 months. Among 28 repairs of Taussig-Bing hearts, 11 patients (39%) died; the mortality rate has not improved over time. Repair that included venous switching was the only risk factor. Of 24 patients repaired, having normally positioned or D-malposed great arteries and noncommitted ventricular septal or complete atrioventricular canal defects, 7 died, 1 among the 11 repairs in the current era. Four with L-malposition underwent repair, with no deaths. Thus current results of repair are good, even in infants, except in patients with Taussig-Bing hearts. In these patients, repair without venous switching is recommended.

Continued on page A43



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Cardioprotective is a word you won't find in standard medical dictionaries.

But you will find it appearing in the medical literature. And you will be hearing it in medical discussions. Until dictionaries recognize the term, MSD invites you to use this as a working definition of *cardioprotective:*

"reduction of the risk of reinfarction and cardiac mortality for many stabilized post-MI patients."

We at MSD feel it is appropriate to bring you this definition of cardioprotective since it was MSD that brought you the impressive clinical data[1] that documented the cardioprotective benefits of BLOCADREN® (Timolol Maleate, MSD) for many stabilized patients who have survived the acute phase of a myocardial infarction.

[1]The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction, N. Engl. J. Med. 304(14):801-807, April 2, 1981.

BLOCADREN is contraindicated in patients with bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see below); cardiogenic shock; and hypersensitivity to this product.

Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after **abrupt** discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart

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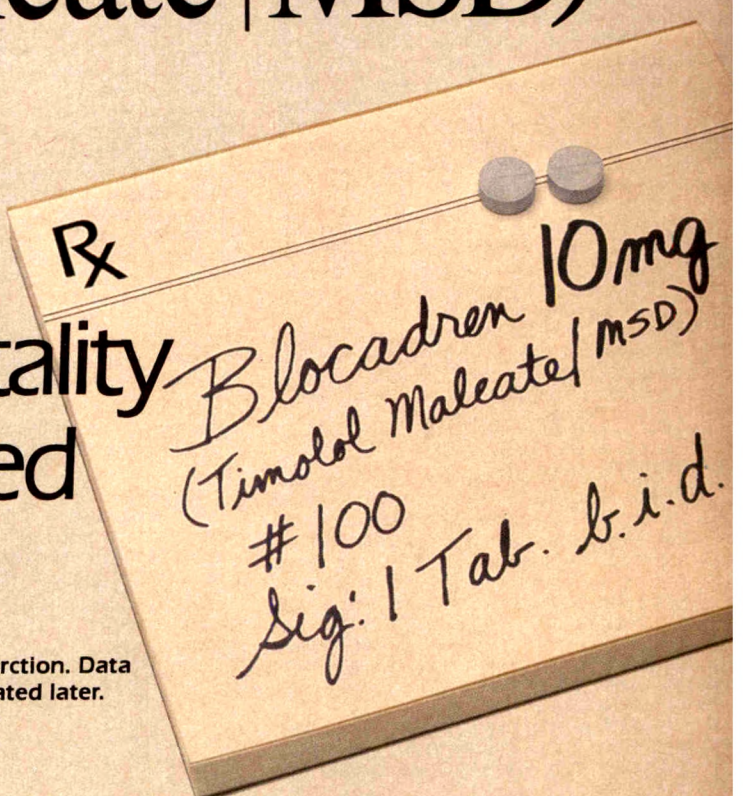
(Timolol Maleate | MSD)

reduces the risk of reinfarction and cardiac mortality for many stabilized post-MI patients

Treatment should be initiated within 1 to 4 weeks after infarction. Data are not available as to whether benefit would ensue if initiated later.



disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

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For a Brief Summary of Prescribing Information, please see next page of this advertisement.

BLOCADREN®
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CONTRAINDICATIONS:

Bronchospasm, including bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS:

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with BLOCADREN should be withdrawn.

In Patients without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

Exacerbation of Ischemic Heart Disease following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: BLOCADREN should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

PRECAUTIONS:

General: *Impaired Hepatic or Renal Function*: Since BLOCADREN is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure: Marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20-mg doses. Dosing in such patients should therefore be especially cautious.

Drug Interactions: Close observation of the patient is recommended when BLOCADREN is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose (1 mg/kg/day). Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose. In a lifetime study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human dose.

Pregnancy—Category C: Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

BLOCADREN is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n=176) %	Placebo (n=168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
INTEGUMENTARY		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, e.g., a group excluding patients with bronchospastic disease, congestive heart failure, or other contraindications to beta-blocker therapy. These adverse reactions can also occur in patients with coronary artery disease.

In a different population, the coronary artery disease population, studied in the Norwegian multicenter trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction†		Withdrawal‡	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure—Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema—Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole*: extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular*: cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive*: gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Endocrine*: hyperglycemia, hypoglycemia; *Integumentary*: rash, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: arthralgia; *Nervous System*: local weakness; *Psychiatric*: depression, nightmares, somnolence, insomnia, nervousness, diminished concentration; *Respiratory*: cough; *Special Senses*: visual disturbances, dry eyes; *Urogenital*: impotence, urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *Nervous System*: reversible mental depression progressing to catatonia; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Cardiovascular*: intensification of AV block (see CONTRAINDICATIONS); *Gastrointestinal*: mesenteric arterial thrombosis, ischemic colitis; *Hematologic*: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; *Allergic*: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; *Miscellaneous*: reversible alopecia, Peyronie's disease. Multisystem syndrome reported with practolol.

Clinical Laboratory Test Findings: Slight increases in blood urea nitrogen, serum potassium, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

1082 (DC7117610)

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For more detailed information, consult your MSD Representative and the Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

CONTENTS

555 Surgical Anatomy of Double-Outlet Right Ventricle—A Reappraisal

ROBERT H. ANDERSON, ANTON E. BECKER, BENSON R. WILCOX, FERGUS J. MACARTNEY, and JAMES L. WILKINSON

The morphology of hearts in which more than half of both arterial valves connect to the right ventricle is reevaluated with surgical considerations. The categorization of these hearts into groups according to the relation of the arterial trunks allows the site of the ventricular septal defect to be inferred. The ventricular septal defect is almost always cradled between the limbs of the septomarginal trabecula; the posteroinferior border may be muscular or membranous. The defect is usually subaortic, sometimes doubly committed and rarely noncommitted in hearts with normally related great arteries. When the great arteries are parallel with the aorta to the right, the defect is usually subpulmonary and rarely doubly committed. The defect is either subaortic or doubly committed when the aorta is to the left of the pulmonary trunk. Cross-sectional echocardiography should provide accurate diagnosis of the anatomy for the surgeons.

560 Percutaneous Balloon Pulmonary Valvuloplasty

ZUHDI LABABIDI and JIUNN-REN WU

Percutaneous balloon pulmonary valvuloplasty (BPV) was performed in 18 consecutive patients with valvular pulmonary stenosis. The patients were aged 11 months to 19 years. The balloons were 12 or 15 mm in diameter and required 100 to 120 pounds/square inch to achieve full inflation when positioned across the stenotic pulmonary valves. Each inflation lasted 10 seconds. Pulmonary valve gradients (ΔP) and cardiac outputs were measured before and 15 minutes after BPV. Significant decrease in ΔP occurred without a decrease in cardiac output. The prevalvuloplasty ΔP dropped from 81 ± 31 to 23 ± 11 mm Hg after BPV ($p < 0.01$). The right ventricular pressure dropped from 106 ± 31 to 50 ± 12 mm Hg ($p < 0.01$). No pulmonary regurgitation was noted. BPV may offer an alternative method for treating pulmonary stenosis.

563 Hemodynamic Responses to Ergometer Exercise in Children and Young Adults With Left Ventricular Pressure or Volume Overload

BRUCE S. ALPERT, DARLENE M. MOES, ROBERT H. DURANT, WILLIAM B. STRONG, and NADINE L. FLOOD

Exercise tests were performed in 137 children and young adults with left ventricular (LV) pressure or volume overload and their data were compared with those from 405 healthy control subjects. By analysis of covariance, the effects of age, race, sex and body surface area were removed. The responses to cycle ergometer stress testing in the patients differed from responses in control subjects for most of the variables studied. The patients with LV volume overload had slightly more impaired responses. The data from the present study do not support those from studies of smaller groups of patients with aortic stenosis that indicated that any exercise variable was predictive of the severity of the LV-to-aorta gradient.

568 Aortic Valve Replacement in Childhood: Evaluation of Left Ventricular Function by Electrocardiography, Echocardiography and Graded Exercise Testing

GEORGE S. BISSET III, RICHARD A. MEYER, STEPHEN S. HIRSCHFELD, FREDERICK W. JAMES, DAVID C. SCHWARTZ, and SAMUEL KAPLAN

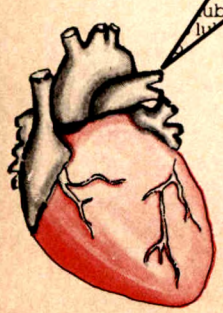
Noninvasive assessment of pre- and postoperative left ventricular function was performed in 15 children who survived aortic valve replacement. Electrocardiography, M-mode echocardiography and graded exercise testing were performed. Patients were grouped according to the dominant lesion preoperatively (aortic stenosis or aortic regurgitation). After aortic valve replacement in patients with aortic stenosis, left ventricular mass remained increased. There was echographic evidence that left ventricular afterload decreased, as demonstrated by a return to normal of the left ventricular shortening fraction. Working capacity and systolic blood pressure responses have remained abnormal for up to 12 years. In patients with aortic regurgitation, the left ventricle remained dilated postoperatively. Septal motion was also abnormal. All patients in this group had ST-segment depression during maximal exercise postoperatively. Aortic valve replacement does not represent curative surgery in the pediatric age group. Most children continue to have evidence of abnormalities of left ventricular performance.

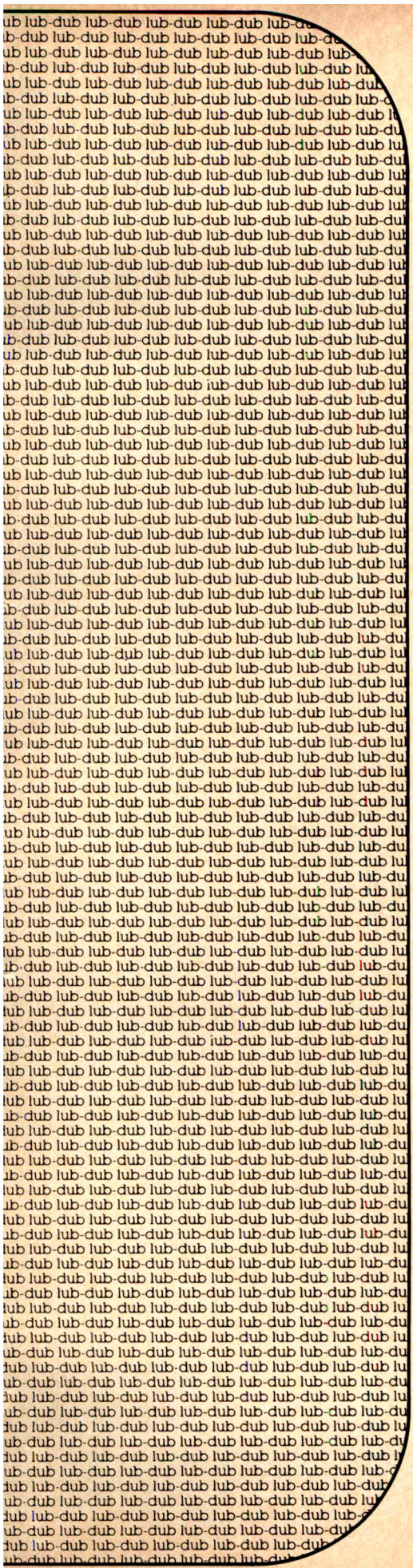
Continued on page A47

25,000,000,000

beats later

and counting





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Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs for overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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The 2nd International Course of Renal Transplantation will be held in Barcelona (Spain) at the Palacio de Congresos on the 12th, 13th, 14th and 15th of December, 1983 directed by Drs. Jose Mª Gil-Vernet, Antonio Caralps, J. Vives, J. Andreu and A. Brulles.

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CONTENTS

573 Double-Inlet Left Ventricle With Rudimentary Right Ventricle and Ventriculoarterial Concordance

ROBERT H. ANDERSON, CORA C. LENOX, JAMES R. ZUBERBUHLER, SIEW Y. HO, AUDREY SMITH, and JAMES L. WILKINSON

Seven hearts with double-inlet left ventricle, rudimentary right ventricle and ventriculoarterial concordance were studied. In 5 hearts, 2 atrioventricular valves were present and 2 hearts had a common atrioventricular valve. The rudimentary right ventricle was obliquely situated on the anterior surface of the left ventricle in 6 cases. One heart had the rudimentary right ventricle in the left-sided position. Conduction tissue studies were performed in 2 hearts. In 1, the distribution was as expected in double-inlet left ventricle, but a different pattern was seen in the other case. These conduction tissue findings are discussed in light of options for surgical repair. The anatomic findings of the study are related to the likely modes of presentation and differential diagnosis. It is suggested that the term "single ventricle" should not be used to describe these hearts because they do possess 2 ventricular chambers.

578 Pulmonary Vascular Development: Normal Values of Peripheral Vascular Structure

SHEILA G. HAWORTH and ALISON A. HISLOP

Uninjected postmortem normal lung tissue from 49 children aged 1 hour to 14 years were studied using quantitative morphometric techniques to assess arterial size, number and muscularity, particularly in the respiratory region of lung. The normal values in this report provide a basis for the evaluation of lung biopsies in childhood.

MISCELLANEOUS TOPICS

584 Biventricular Function in Sickle-Cell Anemia: Radionuclide Angiographic and Thallium-201 Scintigraphic Evaluation

BRUNO V. MANNO, EDWARD R. BURKA, A-HAMID HAKKI, CATHERINE S. MANNO, ABDULMASSIH S. ISKANDRIAN, and ANN MARIE NOONE

The left ventricular (LV) and right ventricular (RV) function at rest and during exercise were evaluated in 10 patients with sickle-cell anemia (SCA). The LV ejection fraction (EF) was normal in 9 patients at rest and in all 10 patients during exercise, whereas only 2 patients had a normal RVEF at rest and during exercise. Rest thallium-201 images from 9 patients showed abnormal RV function in 8. Thus, in adult patients with SCA, LV function is normal, whereas RV function is abnormal in most patients, most likely because of pulmonary vasoocclusive complications of the disease.

588 Effects of Negative Pleural Pressure on Left Ventricular Hemodynamics

SHELDON A. MAGDER, SAMUEL LICHTENSTEIN, and ALLAN G. ADELMAN

Because negative pleural pressures could theoretically affect left ventricular (LV) function, the hemodynamics of the Mueller maneuver (inspirations against closed airways) was studied in 11 patients. This procedure produced an immediate decrease in aortic and left atrial pressures. However, transmural aortic and left atrial pressures (relative to atmosphere) increased markedly. Similar changes occurred during spontaneous breathing. These changes are best explained by right ventricular interference with LV function and impedance to LV ejection by the negative pleural pressure.

METHODS

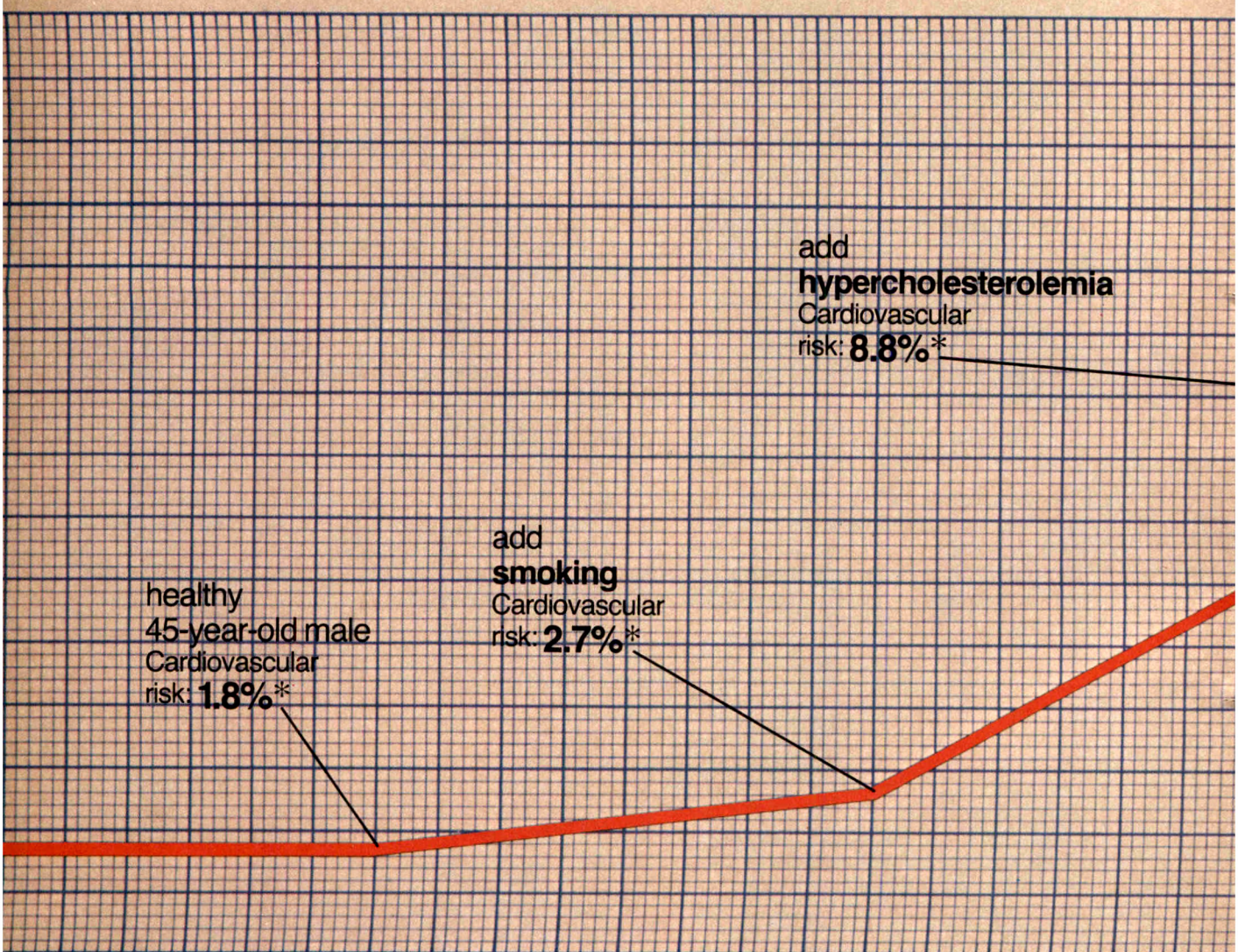
595 Effects of Posture and Respiration on Body Surface Electrocardiogram

DAVID J. SUTHERLAND, DAVID D. McPHERSON, C. ANNE SPENCER, C. SUSAN ARMSTRONG, B. MILAN HORACEK, and TERRENCE J. MONTAGUE, *With the technical assistance of* SHARON A. BLACK *and* SUSAN M. RIGBY

Body surface electrocardiograms (ECGs) were recorded in 36 normal subjects during cyclic respiration in the supine and upright positions, and at static end-tidal inspiration, functional residual capacity, total lung capacity and residual volume. Torso distributions of the time integral of the P wave and QRS and ST segments were determined with a 120-lead electrode array. Changes in ECG distributions were assessed by difference-mapping techniques and the root-mean-square index of variability. Position change from supine to upright and maximal inspiration were associated with inferior spatial shifts of P-wave and QRS torso distributions. Tidal volume respiration was associated with very little change in spatial appearances. The greatest root-mean-square variability occurred between maps at the end points of maximal respiration and was least for tidal volume respiration, with position change having an intermediate degree of variability—in relative terms, P-wave variability > ST > QRS

Continued on page A54

In hypertensive patients:

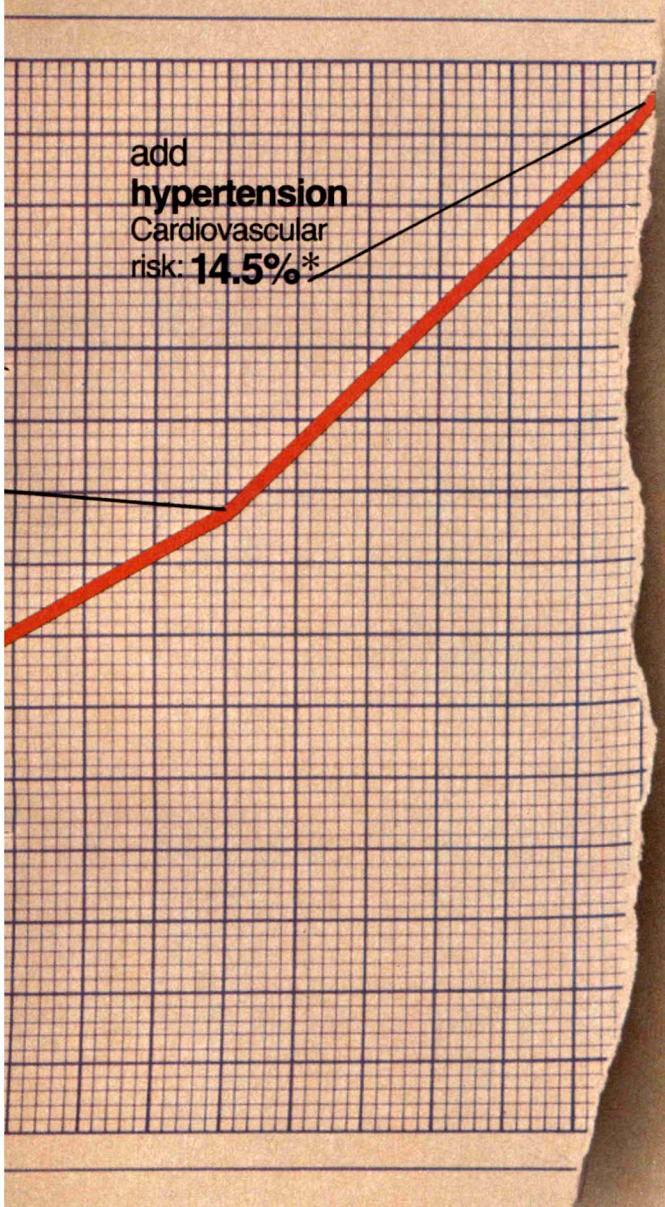


Other risk factors in CHD are diabetes, obesity, lack of exercise, stress, heredity, sex, age, race.

*Percent equals chances in 100 of developing coronary heart disease within 6 years.

Adapted from *Coronary Risk Handbook:* Estimating risk of coronary heart disease in daily practice. 1973, American Heart Assoc., Inc.

Consider the Risks



▪ When selecting antihypertensive therapy, clinical consideration should be given to the effects of the specific drug on coronary risk factors. Blood pressure control should be achieved without adversely affecting blood lipids.

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†Minipress is not indicated for the treatment of hyperlipidemia.

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BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*
INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. O'Conner DJ, Preston RA, Sasso EH: Renal perfusion changes during treatment of essential hypertension: Prazosin versus propranolol. *J Cardiovasc Pharmacol* 1(suppl):S38-S42, 1979. 2. Falase AO, Salako LA: The effect of prazosin combined with a diuretic, polythiazide, in hypertensive Africans. *Curr Ther Res* 25:10-15, 1979. 3. Okun R, Maxwell M: Long-term antihypertensive therapy with prazosin plus a diuretic. *J Cardiovasc Pharmacol* 1(suppl):S21-S27, 1979. 4. Kirkendall WM, Hammond JJ, Thomas JC, et al: Prazosin and clonidine for moderately severe hypertension. *JAMA* 240 (23): 2553-2556, December 1, 1978. 5. Harter HR, Delmez JA: Effects of prazosin in the control of blood pressure in hypertensive dialysis patients. *J Cardiovasc Pharmacol* 1(suppl):S43-S55, 1979. 6. Leren P, Foss PO, Helgeland A, et al: Effect of propranolol and prazosin on blood lipids: The Oslo study. *Lancet*: 4-6, July 5, 1980. 7. Lowenstein J, Neusy A-J: The biochemical effects of antihypertensive agents and the impact on atherosclerosis. *J Cardiovasc Pharmacol* 4 (suppl 2):S262-S264, 1982. 8. Kokubu T, Itoh I, Kurita H, et al: Effect of prazosin on serum lipids. *J Cardiovasc Pharmacol* 4 (suppl 2):S228-S232, 1982. 9. Velasco M, Silva H, Morillo J, et al: Effect of prazosin on blood lipids and on thyroid function in hypertensive patients. *J Cardiovasc Pharmacol* 4 (suppl 2):S225-S227, 1982.

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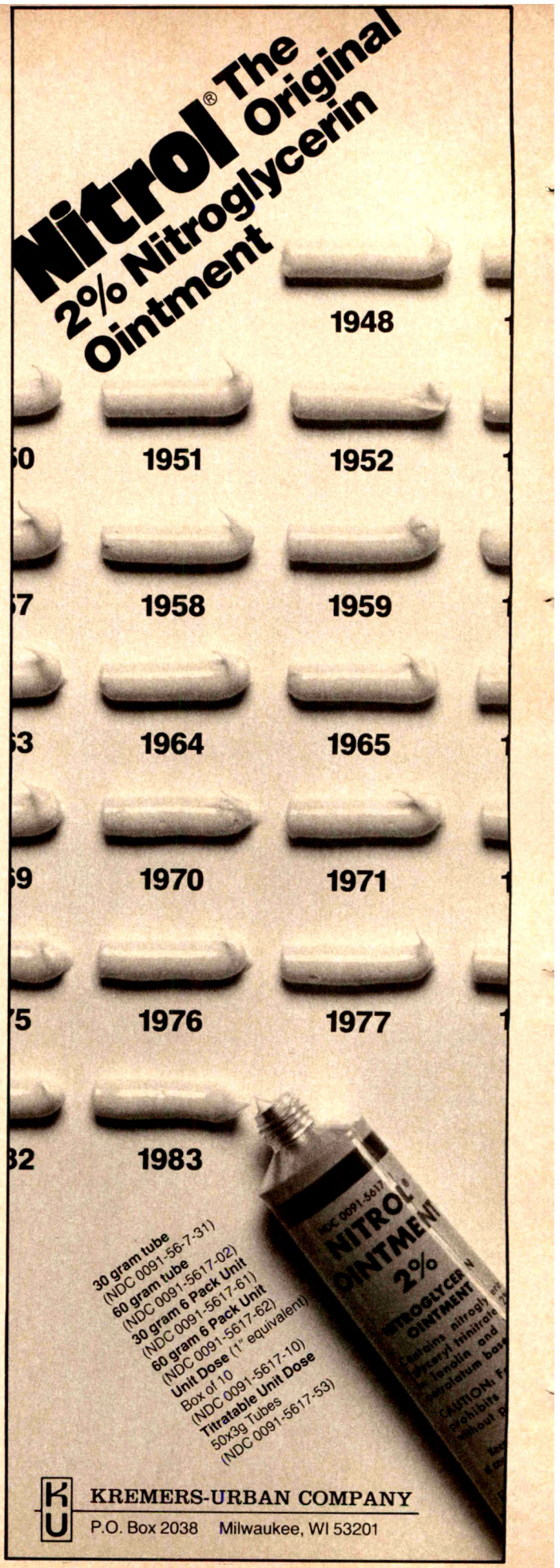

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segments. Thus, resting tidal volume respiration has little effect on body respiration and posture change may, however, be associated with substa in body surface potential map distributions, and their effects should be co volve either factor.

601 An Ambulatory Ventricular Function Monitor: Validation and Prelimina

RICHARD A. WILSON, PAUL J. SULLIVAN, RICHARD H. MOORE, JA NATHANIEL M. ALPERT, CHARLES A. BOUCHER, KENNETH A. McK

A device for the continuous measurement of left ventricular (LV) function ment consisted of 2 arrays of radiation sensitive cadmium telluride detecto left ventricle and lung by a vest-like garment (hence the name VEST). Th cluded analog-to-digital converters, a battery pack, microprocessor and back pack. Data generated by the VEST, including the digitized aver counts/13 ms in each radiation detector, and time since commencement a cassette tape recorder every 2 minutes for subsequent analysis. At the blood pool imaging, the VEST was positioned and worn by the subjects wh ing. The correlation of ejection fraction calculated independently from th was >0.95. The inter-record reproducibility of the ejection fraction measu was <3%.

607 Hydrogen Peroxide Contrast Echocardiography

F. ANDREW GAFFNEY, JUI-CHIN LIN, RONALD M. PESHOCK, LARRY B

There are several echocardiographic contrast agents, but their unreliability vious studies suggest that dilute hydrogen peroxide (H_2O_2) is a safe intrav in contrast echocardiography. To obtain dense opacification reliably, H_2O_2 0.2 μm Millipore filter and diluted with heparinized saline solution to mak blood was withdrawn from an intravenous needle into a syringe containing the contents injected. Studies in dogs, normal adults and 36 patients with dense, sustained opacification with no complications. In vitro mixture of H_2 or plasma produced only a few microbubbles, while addition to whole suggesting that microbubble formation is due to oxygen produced by leuko cardiography is simple and inexpensive, and reliably provides dense, sustai nificant advantages over currently used agents. Caution should be exercis hypertension or large right-to-left shunts because little clinical experienc tients.

EXPERIMENTAL STUDIES

610 Effect of Coronary Reperfusion on Myocardial Hemorrhage and Infarct

CHARLES S. ROBERTS, FREDERICK J. SCHOEN, and ROBERT A. KL

Early coronary reperfusion for treatment of acute myocardial infarction is a result in hemorrhagic infarction. The effect of hemorrhage on the healin reperfusion is unknown, but could be detrimental. To compare repair of ischemic infarcts, 2 coronary arteries were occluded in 14 anesthetized d reperfused. Either 1 or 14 days later, samples from the center of the infarct analyzed for hemoglobin (Hb), creatine kinase (CK) and hydroxyproline co days after coronary occlusion, the myocardium was studied histologically was present in all reperfused infarcts at 1 day; hemoglobin content was 8 10 ± 2 mg/g in permanently ischemic infarcts, but was highest in reperfus versus permanently ischemic infarcts). CK content in reperfused infarcts an similarly depressed (4 ± 2 and 7 ± 1 IU/mg protein, compared with 30 ± 5 p <0.05). At 3 days, polymorphonuclear leukocyte infiltration was less pro permanently ischemic infarcts. At 14 days, hydroxyproline levels were sim μg/mg) and permanently ischemic infarcts (10.7 ± 1.9 μg/mg), and higher μg/mg). Thus, intramyocardial hemorrhage occurs early in reperfused infa nently ischemic infarcts, and is associated with an altered early granulocyte lagen formation.

Continued on page A59

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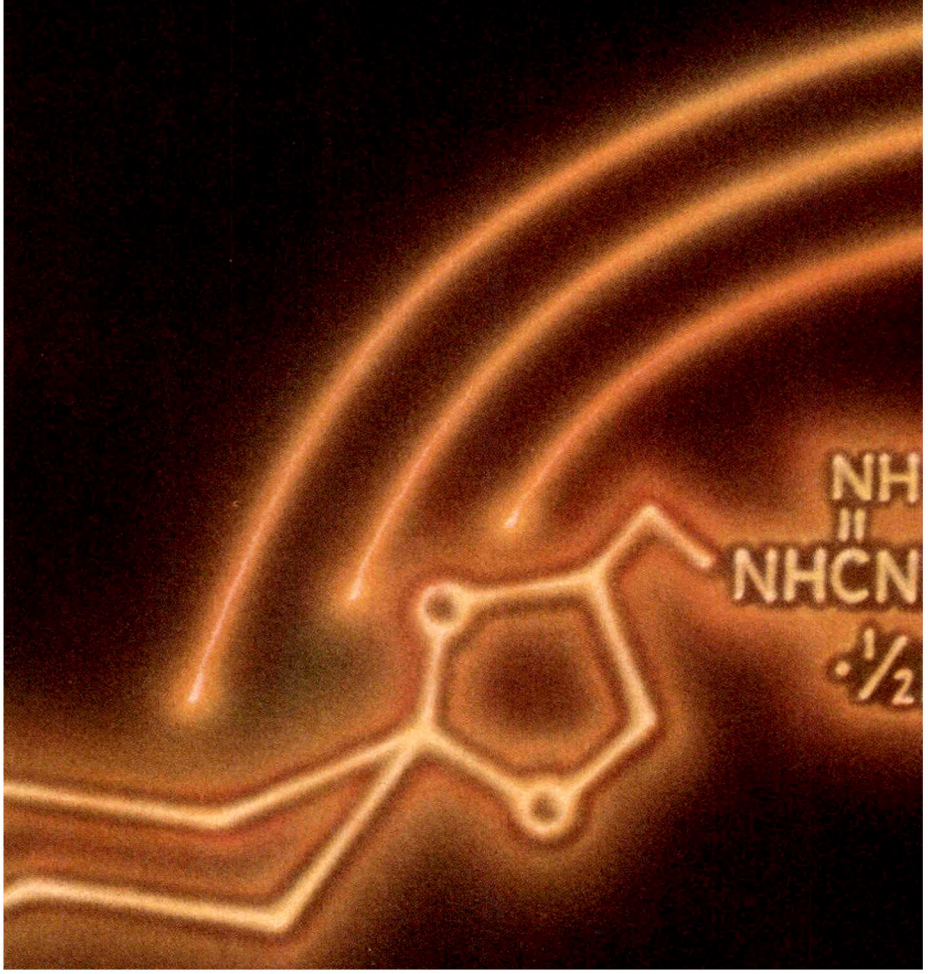

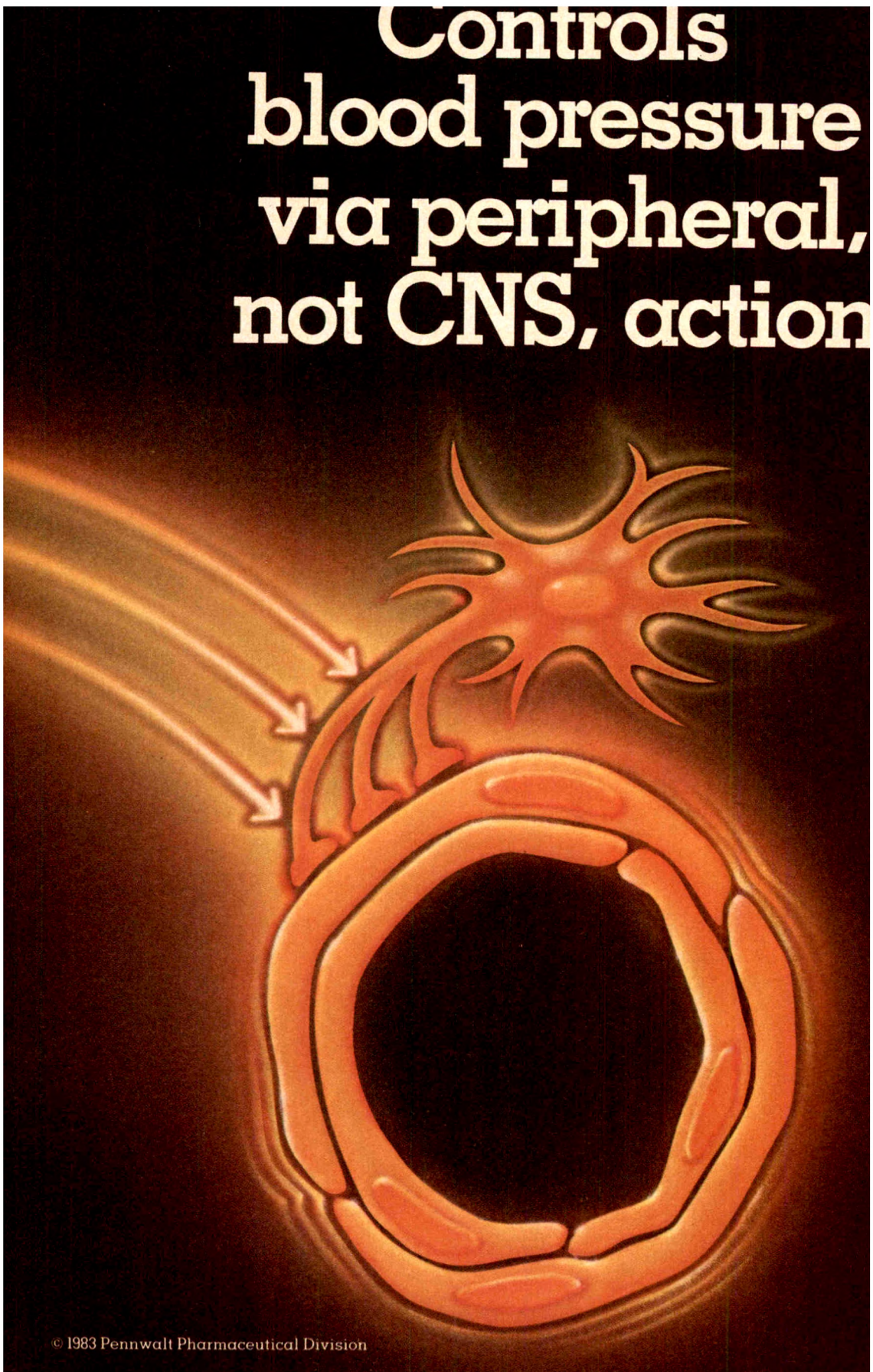
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HYLOREL: A New Peripheral Sympathetic Inhibitor

HYLOREL controls blood pressure via peripheral, not CNS, action... allowing relaxation of the arterioles. Some CNS effects have been reported in patients treated with antihypertensive regimens that included HYLOREL. With a diuretic, HYLOREL is useful in the Step-2 treatment of hypertension.

HYLOREL is a well-tolerated alternative to beta blockers, prazosin, and centrally acting antihypertensives, when a diuretic alone is not enough.

As Effective as Aldomet®*[1]

HYLOREL, in controlled clinical studies, provided blood pressure control comparable to Aldomet, with less drowsiness, depression, and impotence. Patients treated with Aldomet had less diarrhea and fewer orthostatic effects than did those treated with HYLOREL Tablets (guanadrel sulfate).[1]

Orthostatic hypotension, diarrhea, and ejaculation disturbances may occur in patients but seldom have been a cause for discontinuing HYLOREL therapy (see Table 1).

Table 1.
Percent of Patients Discontinuing Therapy

	HYLOREL	Methyldopa	Guanethidine
orthostatic faintness	0.6	0.7	6.0*
syncope	0.4	0.3	2.0
other faintness	1.2	0.0	0.0
increased bowel movements	0.8	0.7	1.4
drowsiness	0.0	1.9*	0.0
fatigue	0.2	2.6*	0.0
ejaculation disturbances	0.4	0.0	0.0
Number of patients analyzed	(481)	(271)	(222)

*Significantly greater than HYLOREL ($p<0.003$).

A Well-tolerated and Useful Choice for Step-2 Treatment of Hypertension

HYLOREL, with a diuretic, is easy to use and economical... for the Step-2 treatment of hypertension.

HYLOREL has not caused a significant change in cardiac output nor adverse effects on liver function.

HYLOREL should not be used in patients with pheochromocytoma nor concurrently with monoamine oxidase inhibitors. HYLOREL should not be given to patients with frank congestive heart failure.

HYLOREL is not contraindicated in patients with ischemic heart disease or peripheral vascular disease.

Two Doses a Day for Most Patients With Hypertension

HYLOREL is prompt acting and rapidly cleared. The dosage can be conveniently titrated. Two doses per day adequately control blood pressure for 24 hours and are associated with minimal morning orthostatic hypotension. Dosage may be adjusted weekly or monthly to fit the patient's needs.

HYLOREL is a Step-2 therapy and should be added to a diuretic regimen for optimal blood pressure control. HYLOREL should be given in divided doses... the usual starting dose is 10 mg per day. The dosage range for most patients is 20 to 70 mg per day.

*Aldomet® is a registered trademark of Merck Sharp & Dohme.

1. Nugent CA, Palmer JD, Ursprung JJ: Guanadrel sulfate compared with methyldopa for mild and moderate hypertension. *Pharmacotherapy* 2:378-383, 1982.

New for hypertension from Pennwalt

Hylorel® 10 & 25 mg Tablets (GUANADREL SULFATE)

Please refer to the brief summary, including Warnings and Adverse Reactions, on the following page.

Hylorel® 10 & 25 mg Tablets
(GUANADREL SULFATE)

Before prescribing see complete prescribing information; a brief summary follows.

DESCRIPTION: HYLOREL Tablets contain guanadrel sulfate—an antihypertensive agent belonging to the class of adrenergic neuron inhibitors.

CLINICAL PHARMACOLOGY: Guanadrel sulfate is an orally effective antihypertensive agent that lowers both systolic and diastolic arterial blood pressures. Guanadrel sulfate inhibits sympathetic vasoconstriction by inhibiting norepinephrine release from neuronal storage sites and also causes depletion of norepinephrine from nerve endings. This results in relaxation of vascular smooth muscle. No significant change in cardiac output accompanies the blood pressure decline in normal individuals.

INDICATIONS AND USAGE: HYLOREL is indicated for the treatment of hypertension in patients not responding adequately to a thiazide-type diuretic. HYLOREL is Step-2 therapy and should be added to a diuretic regimen for optimum blood pressure control.

CONTRAINDICATIONS: Known or suspected pheochromocytoma; concurrently or within one week of the use of monoamine oxidase inhibitors; patients hypersensitive to the drug; patients with frank congestive heart failure.

WARNINGS: Orthostatic Hypotension and its consequences (dizziness and weakness) are frequent in people treated with HYLOREL. Rarely, fainting upon standing or exercise is seen. Patients with known regional vascular disease (cerebral, coronary) are at particular risk from marked orthostatic hypotension, and HYLOREL should be avoided in them unless drugs with lesser degrees of orthostatic hypotension are ineffective or unacceptable.
Surgery—HYLOREL should be discontinued 48–72 hours before elective surgery to reduce the possibility of vascular collapse during anesthesia. If emergency surgery is required, the anesthesiologist should be made aware that the patient has been taking HYLOREL, and that preanesthetic and anesthetic agents should be administered cautiously in reduced dosage. If vasopressors are needed, they must be used cautiously, as guanadrel can enhance the pressor response to such agents and increase their arrhythmogenicity.
Drug Interactions—Tricyclic antidepressants and indirect-acting sympathomimetics can reverse the effects of neuronal blocking agents. IN VIEW OF THE PRESENCE OF SYMPATHOMIMETIC AMINES IN MANY NON-PRESCRIPTION DRUGS FOR THE TREATMENT OF COLDS, ALLERGY, OR ASTHMA, PATIENTS GIVEN GUANADREL SHOULD BE SPECIFICALLY WARNED NOT TO USE SUCH PREPARATIONS WITHOUT THEIR PHYSICIAN'S ADVICE. Drugs that affect the adrenergic response by the same mechanisms as guanadrel sulfate or by other mechanisms would be expected to potentiate the effects of HYLOREL causing excessive postural hypotension and bradycardia. These include alpha or beta adrenergic blocking agents and reserpine. There is no clinical experience with such combinations.
Asthmatic patients with bronchial asthma: need special attention as their condition may be aggravated by catecholamine depletion and sympathomimetic amines may interfere with the hypotensive effect of guanadrel.

PRECAUTIONS: General—Salt and water retention may occur. In clinical studies, major problems did not arise because of concomitant diuretic use. Patients with heart failure and patients with renal failure have not been studied on HYLOREL. HYLOREL should be used cautiously in patients with a history of peptic ulcer.
Carcinogenesis—No evidence of carcinogenic potential appeared in animal studies.
Mutagenesis—Salmonella testing showed no evidence of activity.
Pregnancy Category B
Impairment of fertility and teratogenic effects—Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to HYLOREL. There are no adequate and well-controlled studies in pregnant women. HYLOREL should be used in pregnant women only when the potential benefit outweighs the potential risk to mother and infant.
Nursing mothers—It is not known whether or not guanadrel sulfate is excreted in human milk.
Pediatric Use—Safety and effectiveness of guanadrel in children have not been established.

ADVERSE REACTIONS: The adverse reaction data in this section are derived principally from comparative long-term studies with methyldopa and guanethidine. Side effects were assessed through the use of periodic questionnaires, a method that tends to give high adverse reaction rates. Reasons for discontinuation of therapy are shown in the following table.

PERCENT OF PATIENTS WHO DISCONTINUED THERAPY

	Guanadrel	Methyldopa	Guanethidine
Orthostatic faintness	0.6	0.7	6.0
Syncope	0.4	0.3	2.0
Other faintness	1.2	0.0	0.0
Increased bowel movements	0.8	0.7	1.4
Drowsiness	0.0	1.9	0.0
Fatigue	0.2	2.6	0.0
Ejaculation disturbances	0.4	0.0	0.0

The following percentages represent the number of patients who reported an event at least once over the treatment periods (6 months to 3 years). For such long-term studies, these rates for side effects, often found in untreated people as well as in association with adrenergic neuron blocking agents, tend to be high and accumulate with time. The rates for methyldopa and guanethidine should aid in interpretation of this information. It can be seen that serious consequences of the orthostatic effect of guanadrel, such as syncope were very uncommon.

1544 guanadrel, 330 guanethidine and 743 methyldopa patients were evaluated in comparison studies. The observed incidence rates of major drug-related side effects for guanadrel, guanethidine and methyldopa respectively are as follows: Orthostatic faintness: 49%, 48%, 41%; other faintness: 47%, 45%, 46%; increased bowel movements: 31%, 36%, 28%; ejaculation disturbances:18%, 22%, 21%; impotence: 5.1%, 7.2%, 12.2%; syncope: 0.4%, 2%, 0.3%; urine retention: 0.2%, 0%, 0%. Apart from these adverse effects, many others were reported. Relationship to therapy is less clear, although some (such as peripheral edema with all three drugs, depression with methyldopa) are in part drug related. All adverse effects reported in at least 1% of guanadrel patients are listed in the full prescribing information. (This is a brief summary.)

DOSAGE AND ADMINISTRATION: As with other sympathetic suppressant drugs, the dose response to HYLOREL varies widely and must be adjusted for each patient until the therapeutic goal is achieved. With long-term therapy, some tolerance may occur and the dosage may have to be increased.
Because HYLOREL has a substantial orthostatic effect, monitoring both supine and standing pressure is essential, especially while dosage is being adjusted.
HYLOREL should be administered in divided doses. The usual starting dosage for treating hypertension is 10 mg per day, which can be given as 5 mg b.i.d. by breaking the 10 mg tablet. Because the half-life is approximately ten hours, the dosage should be adjusted weekly or monthly until blood pressure is controlled. Most patients will require daily dosage of the range of 20 to 75 mg usually in twice daily doses. For larger doses 3 or 4 times daily dosing may be needed.

COMBINATION THERAPY: HYLOREL has not been studied in combination with antihypertensive drugs other than thiazide diuretics.

HOW SUPPLIED: HYLOREL Tablets (guanadrel sulfate) are available as follows:
10 mg, scored elliptical tablets (light orange)
Bottles of 100 NDC 0018-0787-71
25 mg, scored elliptical tablets (white)
Bottles of 100 NDC 0018-0788-71

Caution: Federal law prohibits dispensing without a prescription.

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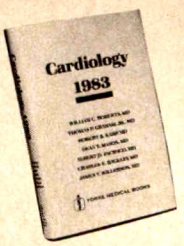

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GRAYSON G. GEARY, LYNNE FENTON, GARY CHENG, GREGORY T. SMITH, BENJAMIN SIU, and J. JUDSON McNAMARA

This study assesses the value of pretreatment with propranolol to reduce ultimate myocardial infarct size after acute coronary artery occlusion in the primate heart. An experimental group of 8 baboons was administered a 2-mg/kg loading dose of propranolol intravenously over a 20-minute period before coronary occlusion. This regimen resulted in a significant decrease in heart rate from 104 ± 19 to 73 ± 8 beats/min ($p < 0.001$), peak rate of increase of left ventricular pressure from 2,300 ± 340 to 1,365 ± 307 mm Hg/s ($p < 0.01$), and cardiac output from 1,571 ± 249 to 1,287 ± 360 ml/min ($p < 0.001$). The left anterior descending coronary artery was occluded for a 2-hour period, after which perfusion was restored. A control group of 8 baboons underwent an identical procedure without propranolol therapy. At 24 hours after occlusion, microvascular dyes were injected into the coronary arteries to delineate the anatomic perfusion bed of the previously occluded coronary artery. This allowed histologically assessed infarct size to be expressed as a percentage of the size of the perfusion bed of the occluded artery. The mean percentage of the perfusion bed infarcted in the control group was 54 ± 14% and in the treated group, 55 ± 21% (difference not significant). Hence, despite a significant decrease in heart rate and left ventricular contractility, pretreatment with propranolol did not reduce ultimate infarct size in the primate heart. The failure of propranolol therapy to result in infarct size reduction in the primate heart may be due primarily to the absence of a significant collateral circulation.

621 Dose-Dependent Electrophysiologic Effects of Amiodarone in the Immature Canine Heart

ARTHUR S. PICKOFF, SHARANJEET SINGH, CELIA J. FLINN, EDDA TORRES, ALAN M. EZRIN, and HENRY GELBAND, *With the technical assistance of* JUDITH KASSNER *and* CARLOS A. FLORES

The electrophysiologic effects of intravenous amiodarone in the intact neonatal canine heart are described. Utilizing standard His bundle recording and stimulation techniques, the effects of 2.5 and 10 mg/kg of amiodarone on sinus and atrioventricular (AV) nodal function as well as atrial and ventricular refractory periods were determined and compared with data obtained in a group of adult dogs. In the neonate, amiodarone resulted in prolongation of sinus cycle length, sinus node recovery time and depressed conduction through the AV node. Atrial and ventricular refractory periods were prolonged in a dose-dependent fashion. The neonate had less depression of AV nodal conduction in response to each amiodarone dose than did the adult, and the neonatal atrium appeared to be more sensitive to amiodarone than the adult atrium.

626 Protection of Turkeys Against Furazolidone-Induced Cardiomyopathy

JUDITH K. GWATHMEY and ROBERT L. HAMLIN

Turkey poults fed furazolidone develop dilated cardiomyopathy within 3 weeks. This is manifested by increased heart weight/body weight ratios and by thinning of both the left ventricular free wall and septum. Birds given propranolol, but not digoxin, are protected from developing the cardiomyopathy.

629 Mechanism of Calcification of Porcine Bioprosthetic Aortic Valve Cusps: Role of T-Lymphocytes

ROBERT J. LEVY, FREDERICK J. SCHOEN, and SUSAN L. HOWARD

Calcification of glutaraldehyde-preserved porcine aortic valve bioprostheses limits their success as cardiac valve substitutes. Previous clinical research has suggested that the host's immune response to the porcine xenograft tissue may contribute to the calcific degeneration. To investigate the possible contribution of the immune response, porcine bioprosthetic cusps implanted subcutaneously in congenitally athymic (nude) BALBc mice and normal controls were analyzed biochemically and histologically after retrieval at 21 days. Calcification was comparable in implants retrieved from athymic and normal mice; porcine bioprosthetic cusp calcium accumulation was similar, and the morphology of the calcification was identical. It is concluded that normal T-lymphocyte function is not necessary for calcification in porcine bioprosthetic cusps and that immunologic processes do not significantly contribute to this process.

632 Formation of Cartilage in Bioprosthetic Cardiac Valves Implanted in Sheep: A Morphologic Study

ELOISA ARBUSTINI, MICHAEL JONES, and VICTOR J. FERRANS

Foci of cartilage were found in 12 of 120 bioprostheses implanted in young sheep for 13 to 24 weeks, but in none of 47 bioprostheses implanted for <13 weeks. Cartilage was found more frequently ($p < 0.01$) in bioprostheses

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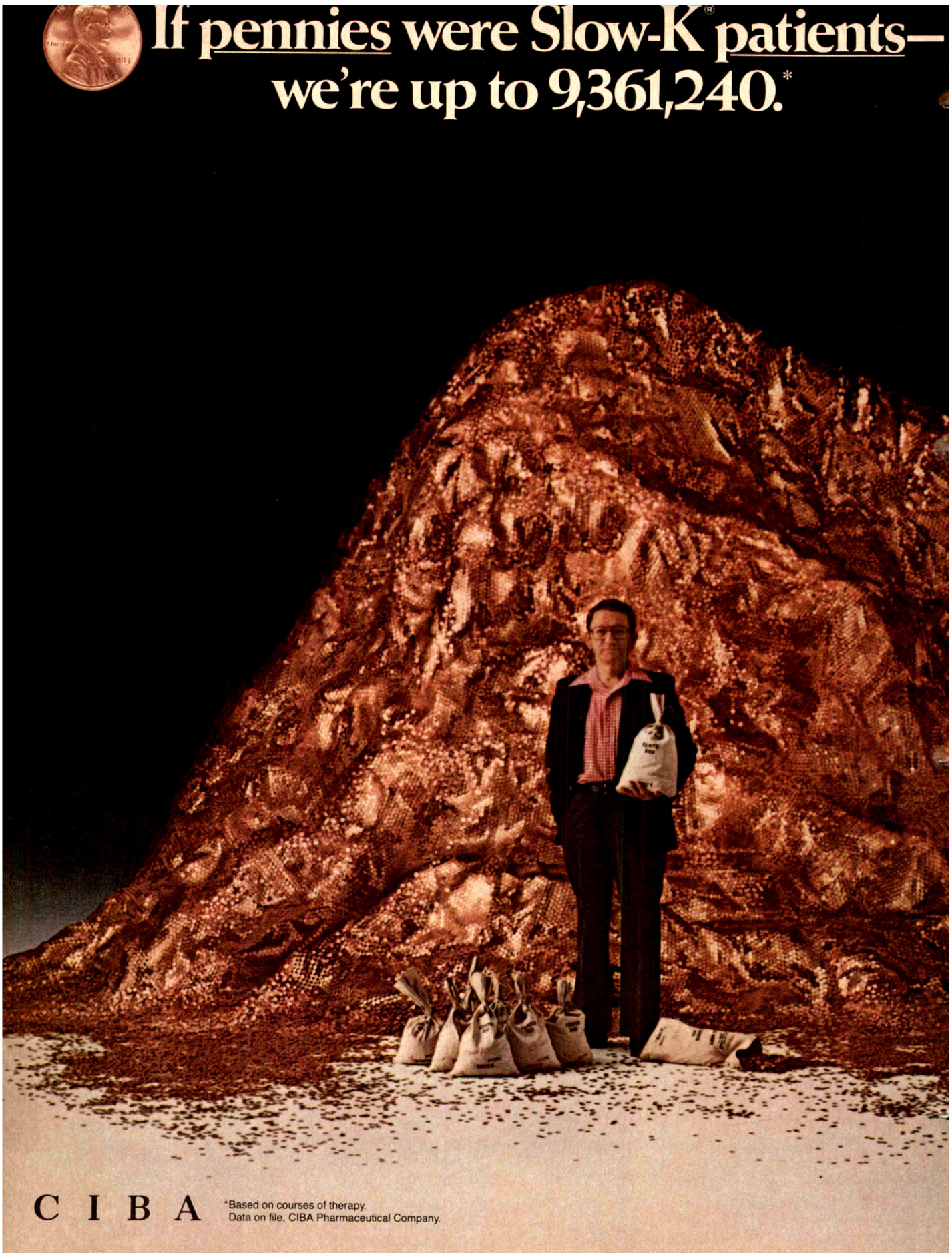
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Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take or have compliance problems with liquid or effervescent potassium preparations, because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

A success from the start—and still growing

Before prescribing, please consult Brief Summary of Prescribing Information on next page.

potassium chloride **slow-release tablets**

Brief Summary of Prescribing Information

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

ADVERSE REACTIONS
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
One of the most severe adverse effects is hyperkalemia (see Contraindications, Warnings and Overdosage). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C82-58 (Rev. 1/83)

Consult complete product information before prescribing.

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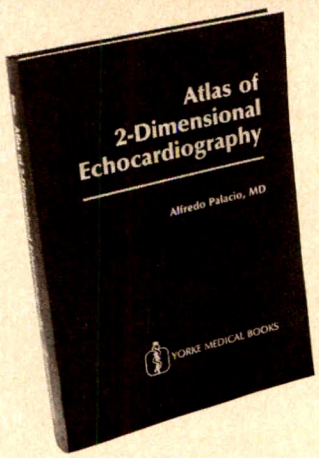

Atlas of 2-Dimensional Echocardiography

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Director of National Institute of Cardiology, Guayaquil, Ecuador
Foreword by David H. Spodick, MD, DSc
Professor of Medicine, University of Massachusetts Medical School;
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implanted in the tricuspid position than in those implanted in the mitral position. In porcine aortic bioprostheses, the cartilage was preferentially localized in the region of the muscle shelf; in pericardial bioprostheses, it occurred in the fibrous sheaths covering the cusps. In both instances, the cartilage was found to undergo calcification, considered to be formed by metaplasia of connective tissue cells of host origin.

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Effect of Interventions in Salvaging Left Ventricular Function in Acute Myocardial Infarction: A Study of Intracoronary Streptokinase

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The ability of intracoronary streptokinase (STK) infused early in acute myocardial infarction (MI) to salvage left ventricular (LV) function was studied in 52 patients who underwent contrast angiography immediately after STK and 6 ± 7 weeks later. Ten nonrevascularized patients had no lysis or reocclusion. Of 42 patients with thrombolysis, 22 with optimal reperfusion underwent coronary artery bypass grafting (CABG) to prevent rethrombosis (STK + CABG group) and 20 did not (STK group). Motion was measured at 100 chords around the left ventricle and expressed in standard deviations (SD) from the normal mean. Hypokinesia was computed as the mean motion of chords in the infarct artery territory and hyperkinesia on the opposite wall was similarly computed. Hypokinesia improved ≥1 SD/chord in 9 STK + CABG patients (41%), 8 STK patients (30%) (p = not significant versus STK + CABG) and 0 nonrevascularized patients. However, the ejection fraction did not change because it was normal in acute MI despite severe hypokinesia due to hyperkinesia on the opposite wall, and a subsequent decrease in hyperkinesia masked significant improvement in hypokinesia. It is concluded that regional wall motion must be measured to adequately assess the effect of therapeutic interventions on LV function. Early thrombolysis in acute MI results in improved LV function. The main benefit of CABG is to prevent rethrombosis.

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Much research has been performed in search of therapeutic interventions that decrease the size of a developing myocardial infarction (MI).[1] Because earlier intervention increases the amount of myocardium salvaged,[2,3] reperfusion using a thrombolytic agent may be of benefit in acute MI. Intracoronary streptokinase results in thrombolysis in 64 to 100% of patients.[4–11] However, it is important to determine whether function improves in the MI region. Therefore, the present study assesses the effect of thrombolysis with streptokinase on global and regional left ventricular (LV) function and measures the correlation between global and regional function.

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Methods

Streptokinase study: We report 52 patients studied by 2 of us (DGM, JS) at University Hospital Eppendorf, Hamburg, West Germany. All had acute MI diagnosed by a history of typical chest pain of <3 hours' duration and ≥2 mm of ST elevation without abnormal Q waves in the leads of ST elevation. Patients with contraindications to thrombolytic therapy or who required resuscitation and had uncertain neurologic status were excluded.

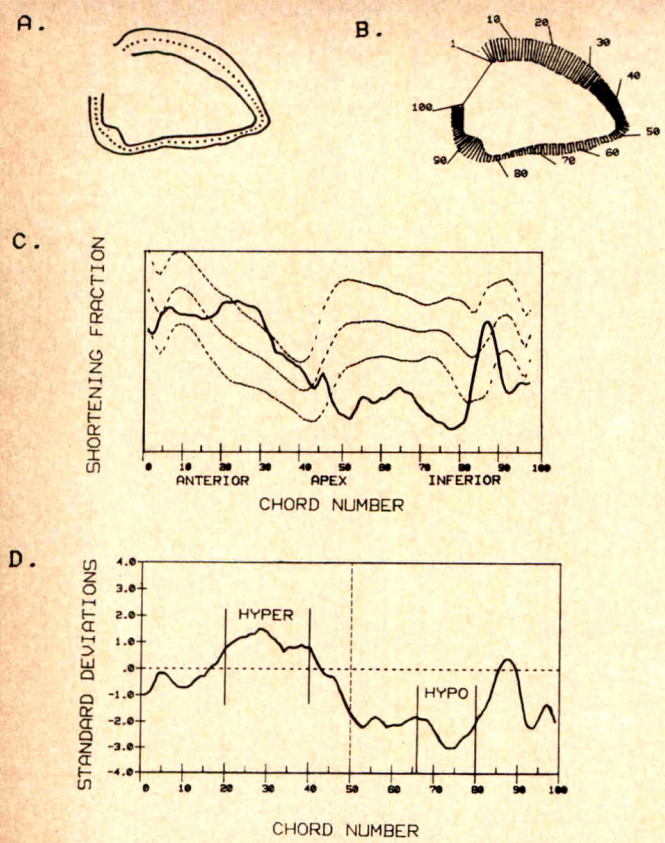

FIGURE 1. Centerline method of analyzing regional left ventricular wall motion. **A,** end-diastolic and end-systolic endocardial contours with centerline. **B,** 100 equidistant chords are constructed perpendicular to the centerline and numbered clockwise from the anterior edge of the aortic valve. The length of each chord is the extent of motion of the corresponding point on the ventricular contour. **C,** wall motion, normalized for heart size (shortening fraction), in a patient (**solid line**) is compared with the motion of the normal group ± 1 standard deviation at each chord. **D,** wall motion of the same patient (**solid line**), plotted in standard deviations from the normal mean (**horizontal dashed line**).

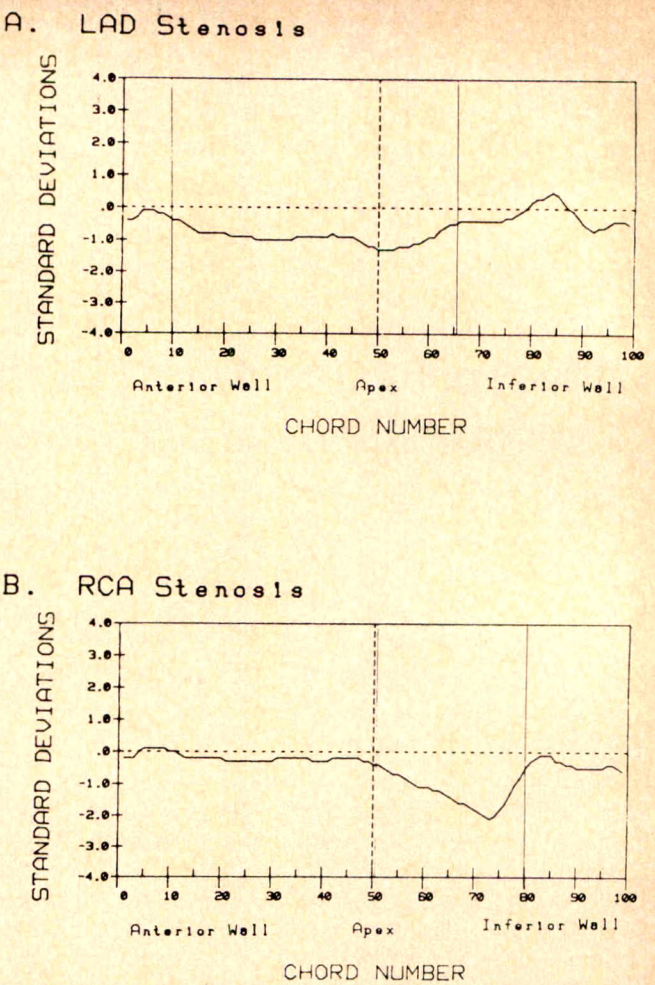

FIGURE 2. Region of the left ventricle affected by stenosis of the left anterior descending (LAD) and right coronary (RCA) arteries. **A,** in patients with isolated stenosis of the LAD, mean wall motion was significantly hypokinetic compared with that in 64 normal patients in the region spanning chords 10 to 66. **B,** in patients with isolated RCA stenosis, mean motion was significantly hypokinetic in chords 51 to 80. SD = standard deviation.

The 52 patients, 44 men and 8 women, represented 30% of all patients admitted with acute MI during the study period and 70% of patients treated with streptokinase. The others had angiograms unsuitable for analysis or refused follow-up study, which was requested in all cases. Mean age was 52 ± 13 years (range 28 to 82). Acute thrombosis involved the left anterior descending coronary artery in 22 patients, the right coronary artery in 23, and the left circumflex artery in 7. Seven patients had previous MI, none <4 months before study and none in the same location as the acute MI.

Coronary angiography was performed by the Judkins technique with hand injection of sodium and meglumine amidotrizoate. Intracoronary nitroglycerin was not given because it was rarely effective.[8] After an intravenous bolus of 10,000 U of heparin, 250,000 U of streptokinase (Streptase, Behring-Werke) were infused at a rate of 4,000 U/min into the ostium of the occluded artery until thrombolysis occurred, then at 2,000 U/min for at least 45 minutes. The usual total dose was 250,000 U (maximum 350,000). Patients received other medication as needed. Left ventriculography was then performed in the right anterior oblique projection using a power injection of 40 ml of contrast through a pigtail catheter. The electrocardiogram score was calculated[12] from standard 12-lead electrocardiograms recorded before streptokinase infusion at a paper speed of 50 mm/s.

In 20 patients, scintigraphy using intracoronary thallium-201 was performed before and after streptokinase therapy in a separate study.[13] Patients who had successful thrombolysis and evidence of myocardial viability by scintigraphy underwent coronary artery bypass surgery (CABG). Patients without scintigrams underwent CABG if no new abnormal Q waves developed after thrombolysis. Thus, patients with optimal reperfusion underwent CABG. Initially, CABG was performed several days after thrombolysis, but in later patients it was performed on the day of thrombolysis because early rethrombosis was occurring. CABG on the day of thrombolysis was not complicated by bleeding. Rethrombosis was diagnosed by repeat coronary angiography in patients who developed chest pain and ST-segment elevation. Angiography was repeated 8 to 230 days after MI (mean 45 ± 49). Cardiac drugs were withheld 24 hours before restudy.

Patients used to validate the method of wall motion analysis: The normal mean and standard deviation (SD) for LV function were defined in a normal reference group of 64 patients studied at the University of Washington or Seattle Veterans Administration Hospitals between 1976 and 1981 who had no coronary artery stenosis ≥50%, history of MI,

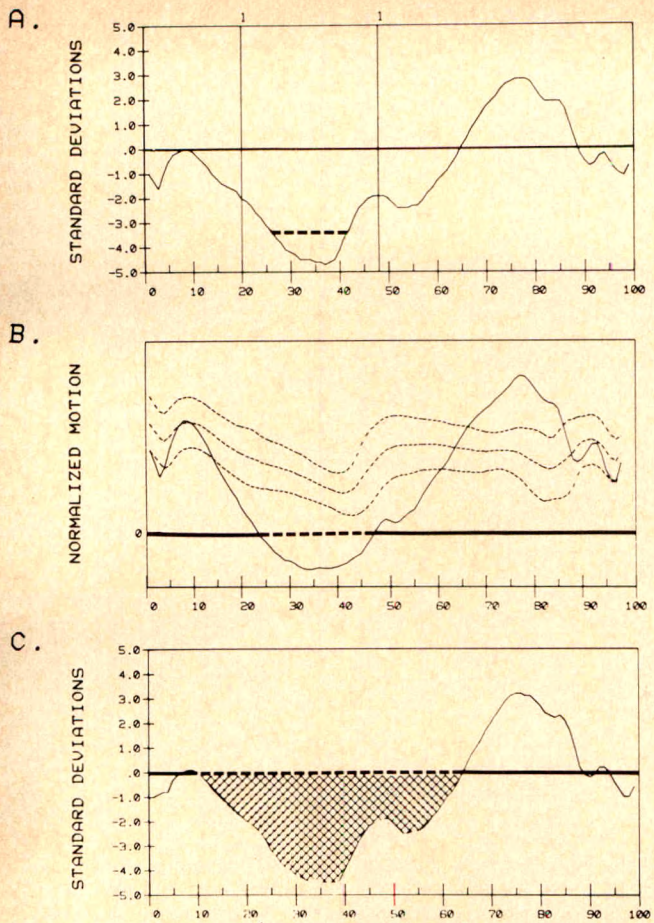

FIGURE 3. Methods of measuring regional wall motion. **A,** patient with isolated occlusion of the left anterior descending artery. The region with most severe hypokinesis is indicated by the vertical lines. The mean chord motion in this region is −3.4 SD, indicated by the **dashed line. B,** in the same patient, the length of the akinetic segment is the number of chords whose motion is 0 or dyskinetic, as indicated by the **dashed portion** of the line at zero motion. **C,** in the same patient, the hypokinetic area (hatched area) is computed by summing the motion of all chords lying within the myocardial infarction artery's territory whose motion is below normal; normal is indicated by the **horizontal line** at 0 standard deviations. The length of the hypokinetic region (**dashed line**) is computed as the number of chords whose motion is less than normal.

sudden death, thoracic surgery or electrocardiographic abnormality other than first-degree atrioventricular block.

The regions of the left ventricle in which motion is affected by stenoses of the coronary arteries were defined in 108 patients (1-vessel disease group) studied at the University of Washington Hospital between 1974 and 1981 who had no history of thoracotomy or valvular or congenital heart disease. Previous MI was present in 32 of 62 patients with stenosis of the left anterior descending coronary artery and in 21 of 46 with right coronary artery stenosis. None had acute MI.

Four methods of wall motion analysis were compared in a separate group of 96 patients (artery group), 49 with chronic stenosis of the left anterior descending or right coronary arteries or both, in whom stenoses could be measured quantitatively, and 47 studied during acute MI.

Analysis of left ventricular volume and regional wall motion: All angiograms were analyzed at the University of Washington. The cinefilms were projected and a normal sinus beat was selected. The end-diastolic endocardial contour was traced from the frame at which the atrial kick was perceived and the end-systolic contour from the frame of minimum volume by visual inspection without operator knowledge of the results of streptokinase therapy. No realignment was performed to correct for cardiac motion within the chest. The contours were entered into a PDP 11/45 computer using an X-Y digitizer. The same observer traced both ventriculograms from each patient. LV volume was calculated by the area-length method.[14] Motion was measured at 100 equidistant chords perpendicular to a center line drawn midway between the end-diastolic contours and numbered clockwise from the anterior aortic valve (Fig. 1).[15] To normalize for heart size, the motion at each chord was divided by the end-diastolic perimeter to yield a dimensionless shortening fraction. Because comparison of different regions requires that motion values be comparable,[16] the normalized motion or shortening fraction (SF_i) of each chord i was converted into units of standard deviations (SD_i) from the normal group mean M_i: $Z_i = (SF_i - M_i)/SD_i$, where Z is expressed in SD (Fig. 1C). If Z is negative, motion is below normal or hypokinetic; a positive Z indicates hyperkinesia.

Wall motion was measured in the region of the LV wall whose function is affected by stenosis of the MI artery (Fig. 2). Artery territories were defined using the 1-vessel disease group. The region of the left ventricle in which mean chord motion in the 62 patients with stenosis of the left anterior descending artery was significantly depressed compared with normal, chords 10 to 66, was defined as that artery's territory. The territory of the right coronary artery was similarly defined as chords 51 to 80 using the mean data of the 46 patients with isolated ≥50% stenosis of the right coronary artery. In patients with stenosis of both arteries, the overlap region was halved and the left anterior descending and right coronary artery territories were assigned chords 10 to 58 and 59 to 80, respectively. In 6 of 7 streptokinase patients with circumflex thrombosis, the hypokinetic region was that of the left anterior descending artery. The seventh patient had a left dominant coronary artery system, and hypokinesia occurred in and was measured in the right coronary artery region.

Hyperkinesia was measured in the chords outside the territory of the MI artery, that is, chords 67 to 80 or 10 to 50 in patients with isolated stenosis of the left anterior descending or right coronary arteries, respectively, and in chords 10 to 58 or 59 to 80, respectively, in patients with stenosis of both arteries. Chords 1 to 10 and 81 to 100 were excluded because of high variability in these regions.[17] Also, chords 81 to 100 overlie the mitral valve.

Within each territory, wall motion was computed as the mean motion of chords lying in the most abnormally contracting region, whose length was restricted to 50% of the territory. This distinguishes patients with coronary artery disease from normal subjects better than motion averaged over longer or shorter regions.[18] Motion in the most hypokinetic region in acute MI was compared with motion in the most hypokinetic region in the second study to avoid regression toward the mean, the bias toward improvement due to the statistical unlikelihood that the same region will be severely abnormal twice.[19]

Study-to-study variability in regional wall motion using the centerline method in patients with stable coronary artery disease is 0.8 ± 0.6 SD/chord in the anterior wall and 0.6 ± 0.4 SD/chord in the inferior wall.[17] Therefore, a change of 1 SD/chord was considered significant.

Comparison of centerline, area and segment length methods: To determine which method of wall motion analysis best detects severe coronary artery stenosis, wall motion measured by the centerline, area and segment length methods was correlated with the severity of coronary artery stenosis assessed quantitatively in artery group patients. Patients with

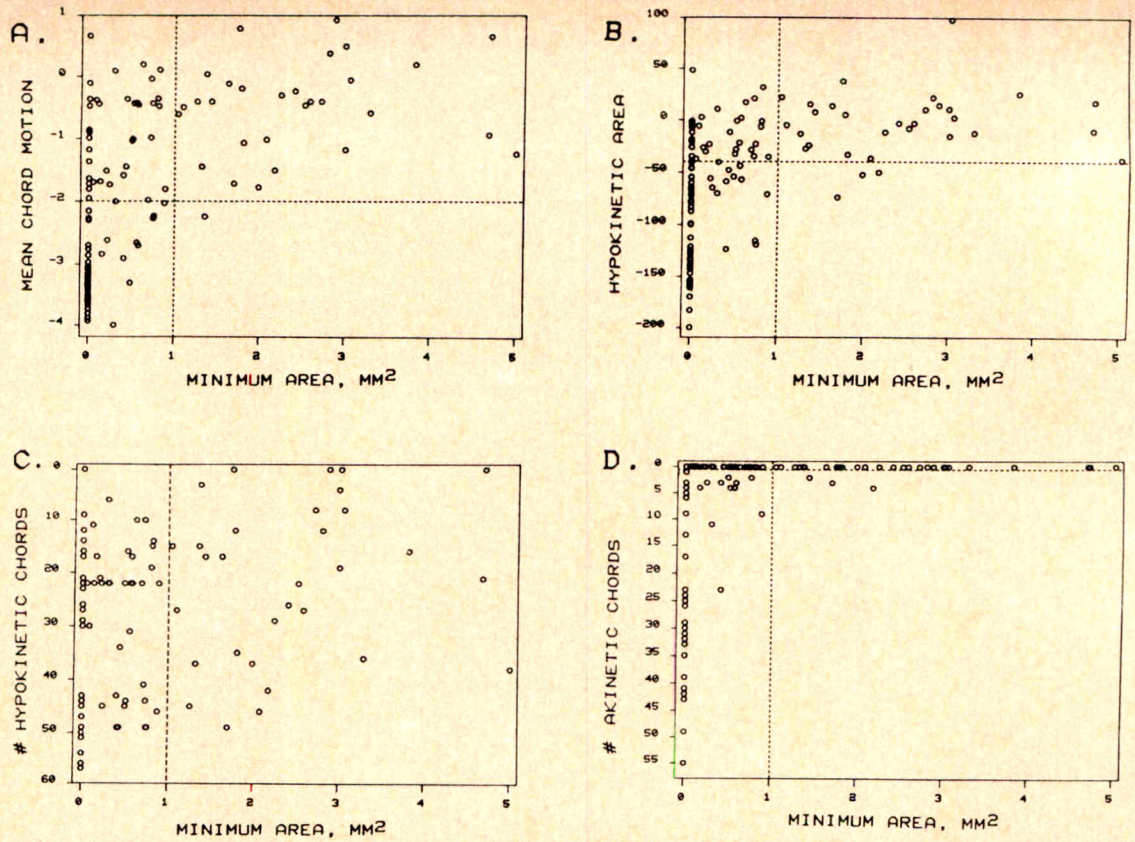

FIGURE 4. Correlation between regional wall motion, measured by 4 methods, and severity of coronary stenosis expressed as the minimum cross-sectional area of the artery lumen at the lesion. **A,** mean chord motion is below −2 standard deviations (SD) in 54 lesions, of which 55 have a minimum area ≤1 mm^2. Thirty-seven lesions have a minimum area ≤1 mm^2 and mean chord motion above −2 SD. **B,** hypokinetic area is below −40 (negative values indicate hypokinesia) in 58 lesions, of which 55 have a minimum area ≤1.0 mm^2. In 36 lesions with a minimum area ≤1 mm^2, the hypokinetic area is above −40 SD chords. **C,** the hypokinetic region has the same length in lesions with minimum area >1.0 and ≤1.0 mm^2. **D,** the akinetic region exceeds 0 chords in length in 49 lesions, of which 46 have a minimum area ≤1.0 mm^2. However, 45 lesions with a minimum area ≤1 mm^2 have no akinesia.

acute MI had total occlusion. In patients with chronic coronary artery stenosis, the minimum cross-sectional area of the stenosis was measured quantitatively using the image reconstruction method.[20] The hypokinetic area was computed by summing the motion of all hypokinetic chords lying within the stenosed artery territory (Fig. 3). The length of the hypokinetic region was computed as the number of chords within the artery territory with less than normal motion. The length of the akinetic segment was measured as the number of chords with motion ≤0.

Statistical analysis was performed using chi-square, 1-way analysis of variance between 3 groups and paired t test.

TABLE I Correlation Between Hypokinesia and Severity of Coronary Stenosis

Method	Stenosis Threshold (mm^2)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Mean chord motion (centerline method)	1.0	59	97	69
	0.5	68	88	76
Hypokinetic area	1.0	60	90	68
	0.5	69	84	75
Akinetic segment length	1.0	49	90	61
	0.5	43	84	68

Results

Comparison of methods of measuring regional left ventricular function: Hypokinesia was correlated with the severity of coronary artery stenosis at 2 thresholds: minimum area ≤0.5 mm^2 and ≤1.0 mm^2 (Fig. 4). These limits approximate the mean plus 2 SD for stenosis in patients with unstable angina and MI.[21] Mean chord motion computed by the centerline method was defined as hypokinetic if depressed more than 2 SD below normal. Chi-square analysis was used to determine the threshold yielding the most significant correlation between hypokinesia and severity of coronary artery stenosis for the other 3 methods. The thresholds were hypokinetic area exceeding −40 SD/chords (Fig. 4B), and akinetic segment length >0 (Fig. 4D). Hypokinetic segment length (Fig. 4C) varied widely and did not correlate with the severity of stenosis. At these thresholds, the sensitivity, specificity, and accuracy of mean chord motion calculated using the centerline method were greater than those of the hypokinetic area and akinetic segment length (Table I). The range for mean chord motion measured by the centerline method, but not for the hypokinetic area, is similar in stenoses of the left anterior descending (0 to −3.2 SD/chord) and right coronary arteries (0 to −4.0 SD/chord) and allows

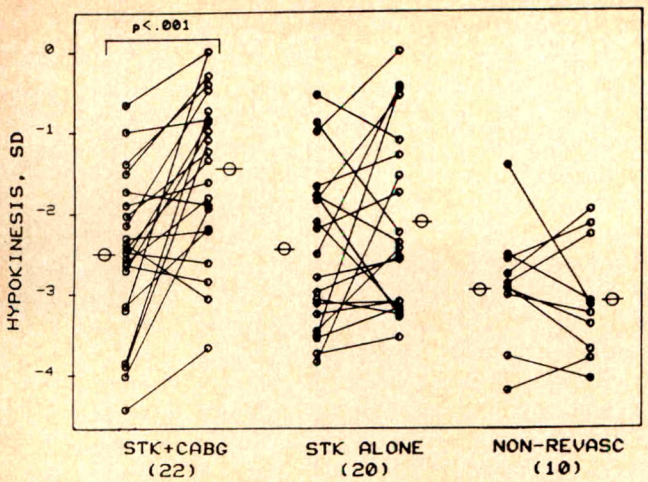

FIGURE 5. Change in hypokinesia in the region of acute ischemia in acute and follow-up studies in each patient group. STK + CABG = patients who had thrombolysis, optimal reperfusion and coronary artery bypass surgery; STK = patients with thrombolysis but who developed Q waves or had large residual perfusion defects on thallium scan; Non-Revasc = patients without thrombolysis or with rethrombosis; SD = standard deviation. The number of patients in each treatment group in shown in parentheses.

them to be analyzed together. Therefore, the centerline method was used to analyze the streptokinase study.

Streptokinase study: The streptokinase (STK) patients were divided into 3 groups. The STK + CABG group consisted of 22 patients who underwent CABG regardless of graft patency at follow-up study. In 10, serial scintigraphy had revealed little or no residual defect. Patients without thrombolysis (n = 5) or with rethrombosis (n = 5) comprised the nonrevascularized group. Those in the STK group (n = 20) had thrombolysis but no CABG because (1) thallium scintigraphy failed to demonstrate myocardial variability (n = 6) or (2) Q waves appeared after reperfusion.

Hypokinesia in the acute study in the 3 groups averaged −2.6 ± 0.9 SD/chord, but mean ejection fraction (EF) was near normal, 55 ± 14% (Fig. 5). In STK + CABG patients, hypokinesia improved ($p < 0.001$) from −2.5 ± 1.0 SD/chord to −1.5 ± 1.0 SD/chord in STK + CABG patients, from −2.5 ± 1.0 to −2.1 ± 1.1 SD/chord (p = not significant [NS]) in STK patients, and became worse from −2.9 ± 0.7 to −3.1 ± 0.7 SD/chord (p = NS; $p < 0.005$ from STK + CABG) in nonrevascularized patients. Only patients with reperfusion had ≥1 SD improvement in hypokinesia (Fig. 6). The improvement in STK + CABG patients was not due to CABG because hypokinesia improved slightly more in patients operated on >24 hours after the onset of chest pain than within 24 hours (1.3 ± 1.2 versus 0.8 ± 1.0 SD/chord, p = NS). In patients whose hypokinesia became worse, the decrease in motion was less severe in the STK + CABG group than in the STK group (−0.3 ± 0.3 versus −0.9 ± 0.5 SD/chord, respectively, $p < 0.05$).

The improved function in the MI region in STK + CABG patients was not reflected by the global EF, which increased only slightly (from 57 ± 15 to 59 ± 13%, p = NS) (Fig. 7). The EF decreased in STK patients from 54 ± 15 to 50 ± 15% (p = NS) and in nonrevascularized patients from 53 ± 4 to 46 ± 6% ($p < 0.005$). The improvement in EF (1.4 ± 9.3%) in STK + CABG patients differed significantly from the decrease in EF in the nonrevascularized group (−6 ± 5%, $p < 0.05$), but not from the decrease in STK patients (−4 ± 9%, p = NS). The EF increased by ≥5% in a similar proportion of STK = CABG patients (7 of 22, 32%) and STK patients (5 of 20, 25%) but in none of the 10 nonrevascularized patients (p = NS).

To determine why the EF failed to reflect the improved wall motion in the MI region, hyperkinesia on the wall opposite the acute MI was measured. Hyperkinesia averaged 1.1 ± 1.1 SD/chord, significantly higher ($p < 0.005$) than the 0.4 ± 0.6 SD/chord measured in patients with chronic coronary artery disease selected from University of Washington files and matched with the streptokinase patients by sex, location of coronary artery stenoses, and previous MI. Hyperkinesia decreased in all 3 groups, from 1.1 ± 1.0 to 0.8 ± 0.9 SD/chord in STK + CABG patients, from 1.2 ± 1.2 to 0.3 ± 0.6 SD/chord ($p < 0.001$) in STK patients, and from 0.9 ± 0.8 to 0.4 ± 5 SD/chord in nonrevascularized patients (Fig. 8). Hyperkinesia decreased by ≥1 SD/chord in a similar proportion of patients in all 3 groups (5 of 22, 7 of 20, and 1 of 10, respectively, in STK + CABG, STK and nonrevascularized). Hyperkinesia in acute MI was similar in patients who did and in those who did not require catecholamine support (1.1 ± 1.2 SD/chord, n = 8, versus 1.0 ± 1.0 SD/chord, n = 44). The decrease in hyperkinesia between studies was also similar in these 2 subgroups (−0.8 ± 1.4 versus −0.5 ± 0.9 SD/chord, respectively).

Although mean hyperkinesia decreased in the group as a whole, hyperkinesia increased in 8 patients, by ≥1 SD in 4 patients. The increase in hyperkinesia was not

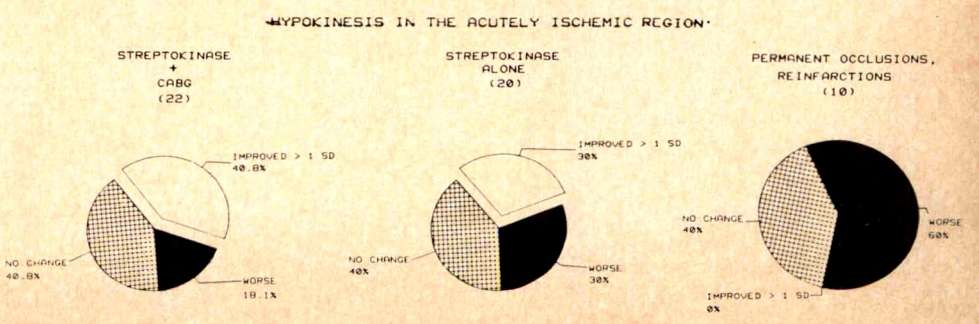

FIGURE 6. Hypokinesia in the acutely ischemic region—the proportion of patients in each group in whom hypokinesia improved by ≥1 standard deviation (SD) (Improved, **white area**), did not change or improved by <1 SD (No Change, **hatched area**), or worsened (Worse, **black area**) in the interim between acute and follow-up studies. Abbreviations as in Figure 5.

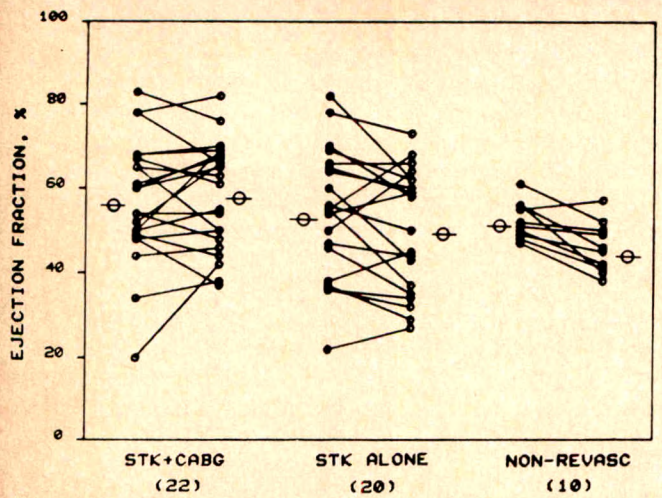

FIGURE 7. Change in ejection fraction in acute and follow-up studies in each patient group. Abbreviations as in Figure 5.

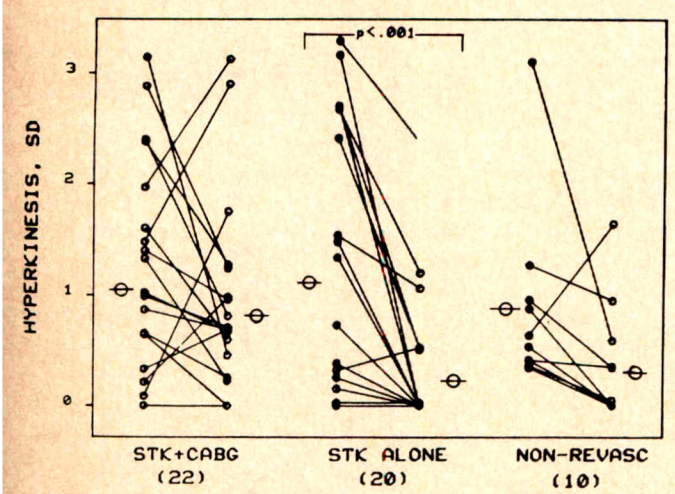

FIGURE 8. Change in hyperkinesia on the wall opposite the acutely ischemic region in acute and follow-up studies in each patient group. Abbreviations as in Figure 5.

significantly related to the initial severity of or change in hypokinesia, patient age, duration of occlusion, MI artery or treatment group, although it was slightly more common in patients with 1-vessel coronary disease, and the percent of stenosis assessed visually in the artery opposite the MI was lower (18 ± 35) in patients with ≥1 SD increase in hyperkinesia than in those without an increase (34 ± 41%, p = NS) (stenosis was coded as 0% if successfully bypassed).

The present study was not a randomized trial of streptokinase. However, the 3 patient groups were similar in severity of disease (Table II).

The time from onset of chest pain to thrombolysis (or to cessation of streptokinase in nonreperfused patients) did not correlate with the change in hypokinesia or EF, perhaps because it was short (mean 3.0 ± 1.0 hours). Indeed, no factor could be identified that predicted success in achieving thrombolysis.

Discussion

Many methods have been developed to measure regional LV function from contrast angiograms.[16,22–24] The centerline method was designed to avoid some inadequacies of the older methods. First, the centerline method uses no coordinate system and does not assume that the LV walls contract toward a central long axis or point. Second, motion is measured on a continuous scale. In contrast, measurement of the percent of the LV circumference[24] that is akinetic or below an arbitrary threshold such as −2 SD limits interpretation of the data, decreases accuracy because variability in the measurement could push a value across the threshold in the absence of real change or hide a significant change because it fails to cross the threshold,[19] and implies without justification that a localized but severe motion abnormality is more significant than an extensive abnormality of only moderate (below threshold) severity. Third, variability is reduced in the centerline method because identification of the apex as a landmark is not required. This may cause inaccuracy in methods based

TABLE II Streptokinase Patient Groups

	STK + CABG	STK	Nonrevascularized
Patient age (yr)	52 ± 12*	54 ± 16	50 ± 11
Males/females	20/2	17/3	8/2
Infarct artery			
Left anterior descending	9	8	5
Right coronary artery	11	7	5
Circumflex	2	5	0
Coronary arteries with stenoses ≥50% (n)			
1	9	10	6
2	7	2	0
3	6	8	4
Duration of occlusion† (h)	2.9 ± 0.8	3.0 ± 1.3	3.2 ± 0.9
QRS score	2.3 ± 2.7	2.8 ± 2.4	2.8 ± 2.8
Q ≥0.03 second in lead of ST elevation	8	9	5
LV function in acute study			
Ejection fraction (%)	57 ± 15	54 ± 15	53 ± 4
Hypokinesia, SD/chord	−2.5 ± 1.0	−2.5 ± 1.0	−2.9 ± 0.7
Hyperkinesia, SD/chord	1.1 ± 1.0	1.2 ± 1.2	0.9 ± 0.8

* Mean ± standard deviation.
† From onset of chest pain to reperfusion or to cessation of streptokinase infusion in nonrevascularized patients.
LV = left ventricular; STK = streptokinase; STK + CABG = streptokinase + coronary bypass graft surgery; nonrevascularized = patients without thrombolysis or with rethrombosis.

on rectangular or radial coordinate systems because the apex is sometimes poorly visualized.[17] Variability is further minimized in the centerline method because motion is averaged over the region of interest.[17] Fourth, the region of interest can be defined precisely. As a result, the discriminant power of the centerline method equals or exceeds that of other methods, as shown in the present study and in a previous report.[25]

In analyzing serial studies, the most hypokinetic regions in the 2 studies were compared. The chord number of the most hypokinetic region varied by <5% of the endocardial contour length. Actually, because the left ventricle lacks anatomic landmarks, it is impossible to identify regions and assign them the same chord number twice by any method of wall motion analysis. A change in ventricular shape, as with dilatation or regional changes in contractility, would cause renumbering because of relative change in centerline length, shifting origin in methods based on center of mass, or shifting apex in coordinate system methods. For these reasons, a region may have a different chord number when restudied. Conversely, comparison of the most hypokinetic region in the acute study with the region of the same chord number in the second study does not guarantee that the same point on the left ventricle was studied, regardless of the method of analysis used, and risks statistical bias toward improvement due to regression toward the mean.[19]

In the present study the EF underestimated both the severity of hypokinesia in acute MI and the improvement in patients with optimal reperfusion (STK + CABG group) because hyperkinesia decreased on the wall opposite the MI. The EF decreased in the STK group despite a small improvement in hypokinesia due to a significant decrease in hyperkinesia. Thus, full assessment of LV function requires analysis of both hypokinesia in the infarct region and hyperkinesia in the opposite wall.

Improvement in regional hypokinesia after successful thrombolysis by streptokinase has been reported.[4–6,10] Our results indicate that streptokinase improves wall motion in the infarct region in some patients, but other factors are also involved. One factor is prevention of rethrombosis, our motive for recommending CABG. None of the patients with rethrombosis had ≥1 SD/chord improvement in hypokinesia. Although mean motion improved only in the STK + CABG group, it is unlikely that CABG effected that improvement because: (1) Patients recommended for CABG had better reperfusion that non-CABG patients who had residual perfusion defects on the thallium scan or developed new Q waves on the electrocardiogram. (2) To salvage myocardium, revascularization must be performed early.[2,3] (In this study almost half the patients had CABG >24 hours later, yet improved more than those operated on the day of MI.) (3) The proportion of patients who improved by at least 1 SD/chord was similar in reperfused patients who did or did not undergo CABG. Thus, the main benefit of CABG may be to prevent rethrombosis.

A second factor determining improvement after reperfusion may be the severity of residual stenosis in the MI artery. If flow-restricting, ischemia may continue because of selective underperfusion of the subendocardium.[26]

Third, angiographic reperfusion of the epicardial coronary arteries is not equivalent to microvascular reperfusion; persistence of a scintigraphic perfusion defect may be analogous to the no-reflow phenomenon[27] and may indicate that necrosis has begun. Finally, collateral circulation may prolong the period of ischemia tolerated before necrosis begins.[6] Further work is needed to clarify these points and, more importantly, to better define the population of patients most likely to benefit from thrombolytic therapy.

Hyperkinesia in the wall opposite the MI has previously been reported[28] and attributed to a Frank-Starling mechanism or to catecholamine release. Hyperkinesia may also be due to unloading of the normal wall due to the decreased contractile force exerted by the MI region. Failure by some[4,29] to document hyperkinesia is probably due to the different methods of wall motion analysis used, because the centerline method is more sensitive in detecting hyperkinesia than either radial or rectangular coordinate methods.[25]

The increase in hyperkinesia in some patients may be due to the development of chronic compensatory hyperkinesia, which has been described months after an MI and is associated with better global function.[30] Biochemical studies in animals suggest that hyperkinesia develops because of hypertrophy.[29] The factors that determine whether a patient will develop chronic hyperkinesia are unclear. Chronic hyperkinesia tended to occur more frequently in patients without severe stenosis of the artery opposite the site of infarct, but was unrelated to the severity of hypokinesia in the infarct region.

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Hemodynamic Effects of Intravenous Prostacyclin in Stable Angina Pectoris

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Prostacyclin (PGI_2) is a naturally occurring vasodilator and inhibitor of platelet aggregation that produces vasodilatation of the systemic, pulmonary and coronary vascular beds in animal models. Because the endogenous production of PGI_2 is reduced in those with coronary arterial disease (CAD), it may have a therapeutic role in patients with ischemic heart disease. To assess its safety and efficacy in this clinical setting, 17 patients with stable angina and CAD received an incremental intravenous infusion of either PGI_2 ($n = 10$) to a maximum dose of 10 ng/kg/min (average 9.8 ± 0.8 [mean ± standard deviation]), or diluent buffer solution (placebo) ($n = 7$). All patients who received PGI_2 became flushed, but experienced no other adverse effects. PGI_2 caused an increase in heart rate (66 ± 11 to 80 ± 11 beats/min, $p < 0.001$) and cardiac index (2.88 ± 0.65 to 3.97 ± 1.17 liters/min/m^2, $p < 0.001$) and a decrease in mean femoral arterial pressure (96 ± 18 to 86 ± 11 mm Hg, $p < 0.001$), but no change in mean pulmonary arterial or capillary wedge pressure. Total systemic and pulmonary vascular resistance decreased significantly ($p < 0.001$). In response to PGI_2, mean coronary sinus blood flow did not change significantly (100 ± 40 to 121 ± 52 ml/min), but coronary vascular resistance decreased (1.07 ± 0.40 to 0.83 ± 0.36 U, $p < 0.001$). No variable was altered by placebo infusion. PGI_2 caused a marked increase in 6-keto $PGF_{1\alpha}$ (the stable metabolite of PGI_2) concentrations in both arterial (42 ± 29 to 567 ± 216 pg/ml, $p < 0.001$) and venous (46 ± 31 to 604 ± 229 pg/ml, $p < 0.001$) blood but no demonstrable change in plasma renin activity. Thus, intravenous PGI_2 to a dosage of 10 ng/kg/min is a safe and effective systemic, pulmonary and coronary arterial vasodilator in patients with CAD and stable angina pectoris.

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Prostacyclin (PGI_2), a naturally occurring vasodilator and inhibitor of platelet aggregation, is synthesized from arachidonic acid by vascular endothelial cells.[1–7] When administered intravenously or intraarterially, it causes systemic and pulmonary vasodilatation.[8] Recent studies demonstrate that intravenous PGI_2 infusion may be efficacious in several conditions, including congestive heart failure[9] and pulmonary hypertension.[10] In systemic atherosclerosis, endogenous PGI_2 production is reduced,[11,12] and its intravenous infusion may provide symptomatic improvement in patients with advanced peripheral vascular disease and rest pain.[13] Similarly, endogenous PGI_2 production is diminished in patients with coronary artery disease (CAD).[14] This observation, in conjunction with the finding in animals that this substance causes coronary arterial vasodilation,[5,15,16] suggests a therapeutic role for PGI_2 in patients with various CAD syndromes such as unstable angina and acute myocardial infarction. However, before it is widely used in such patients, its effects on systemic, pulmonary and coronary hemodynamics require elucidation. Therefore, the present study was performed to assess the influence of an incremental-dose intravenous PGI_2 infusion on cardiac output, coronary blood flow, intracardiac filling pressures and vascular resistance in patients with CAD and stable angina pectoris.

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TABLE I Clinical Data and Effects of Prostacyclin

Pt	Heart Rate (beats/min)		CI (L/min/m²)		FA (mm Hg)		DP × 10³ (Units)		TSVR (dynes s cm⁻⁵)		TPVR (dynes s cm⁻⁵)		CS Flow (ml/min)		CVR (units)		Medications	Percent of CAD Narrowing			
(n)	B	Peak	B	Peak	B	Peak	B	Peak	B	Peak	B	Peak	B	Peak	B	Peak		R	LAD	LC	LD
Prostacyclin Group																					
1	57	72	2.50	3.26	81	72	6.3	7.6	1,234	841	213	164	92	97	0.88	0.74	C, β, N	100	60	75	...
2	55	72	2.18	3.42	83	92	6.1	9.0	1,417	1,001	256	196	76	92	1.09	1.00	β, N	99	75	75	...
3	91	104	2.95	4.60	83	82	9.7	11.4	1,047	706	228	164	66	94	1.26	0.87	β, C, H	...	75	75	...
4	79	90	3.45	4.69	115	105	12.4	13.1	1,441	968	276	175	168	224	0.68	0.47	N, β	...	90	90	75
5	63	75	2.69	3.57	105	90	9.8	9.8	1,735	1,120	347	261	53	54	1.98	1.67	C, β, N, H	75	...		
6	59	68	2.47	3.77	97	80	8.4	7.7	1,848	999	419	225	130	119	0.75	0.67	C, β, N, H	...	100	75	...
7	65	80	2.87	3.45	86	75	7.9	8.5	1,737	1,260	424	386	62	72	1.39	1.04	C β, F	100	99	60	60
8	72	84	3.14	3.72	73	73	7.0	8.2	949	801	233	219	92	158	0.79	0.46	β, N, F	100	50	...	75
9	59	68	2.23	2.49	130	100	12.0	10.9	2,879	1,983	443	258	160	120	0.81	0.83	C, β	90	...	...	60
10	64	84	4.35	6.76	105	90	9.6	10.7	1,306	720	137	96	99	182	1.06	0.50	...	...	70	...	...
Mean	66	80	2.88	3.97	96	86	8.9	9.7	1,559	1,040	298	214	100	121	1.07	0.83	...	...	...	...	...
± SD	11	11	0.65	1.17	18	11	2.2	1.8	550	375	105	78	40	52	0.40	0.36	...	...	...	...	...
P	<0.001		<0.001		<0.01		NS		<0.001		<0.001		NS		<0.001		...	...	...	...	...
Placebo Group																					
11	61	64	2.66	2.74	100	98	8.7	9.0	1,285	1,223	218	225	71	70	0.86	0.91	...	100	...	...	...
12	88	84	2.89	2.85	102	104	11.9	11.6	1,306	1,351	282	247	107	121	0.82	0.69	N	100	50	...	...
13	72	68	1.95	1.88	90	93	9.8	9.5	2,257	2,416	351	442	64	65	1.13	1.05	C, N	...	75	90	90
14	60	56	1.83	1.83	108	110	8.5	9.0	3,000	3,055	472	556	69	93	0.87	0.60	C, β, N, H	...	75	...	...
15	68	64	3.86	3.96	80	79	7.3	7.0	1,658	1,595	207	202	67	61	1.19	1.30	N	...	99	...	99
16	60	56	2.63	2.32	95	93	7.6	7.3	1,529	1,691	273	327	118	123	0.81	0.76	C, N	...	95	...	...
17	72	72	2.04	2.16	100	101	9.9	10.2	2,204	2,104	419	458	126	134	0.80	0.75	N, β	100	90	100	...
Mean	69	66	2.55	2.53	96	97	9.1	9.1	1,962	2,011	331	368	78	87	0.92	0.81	...	...	...	...	...
± SD	10	10	0.71	0.74	9	10	1.6	1.6	827	878	109	159	20	26	0.14	0.21	...	...	...	...	...
P	NS		NS		NS		NS		NS		NS		NS		NS		...	...	...	...	...

B = baseline; β = beta-blocking drug; C = calcium antagonist; CI = cardiac index; CS = coronary sinus; CVR = coronary vascular resistance; DP = heart rate-systolic pressure double product; F = furosemide; FA = femoral artery; H = hydrochlorothiazide; LAD = left anterior descending; LC = left circumflex; LD = left diagonal; N = nitrates; R = right; TPVR = total pulmonary vascular resistance; TSVR = total systemic vascular resistance.

Methods

Patients: The study was performed in 17 patients (10 men, 7 women, mean age 51 years) with angiographic evidence of CAD (≥70% luminal diameter narrowing of ≥1 major coronary arteries) and stable angina pectoris. Informed consent was obtained from all patients. Patients with recent myocardial infarction or a bleeding tendency were not eligible. All data were collected before the introduction of radiographic contrast material and the systemic administration of heparin. Nitroglycerin was not administered during the catheterization procedure. Each patient was randomly assigned to receive 1 of 2 agents: PGI_2 (n = 10) or glycine buffer solution (placebo) (n = 7). The clinical characteristics of the patients assigned to PGI_2 were similar to those of the patients who received placebo (Table I).

Study protocol: In each patient, a thermodilution catheter (model CCS-7N-90B, Wilton Webster Laboratories) was advanced to the coronary sinus from the right basilic vein and its position was confirmed fluoroscopically and oximetrically. The flow-measuring thermistor was positioned just inside the ostium of the coronary sinus on the basis of the fluoroscopic assessment of the position of the ostium. Once the thermistor had been positioned satisfactorily and a test measurement of coronary sinus flow made to confirm that the thermistor was indeed in the coronary sinus and not in the right atrium, the catheter was not moved until all measurements had been completed. A No. 8 Fr sheath fitted with a hemostatic valve and side port extension (Cordis Corporation) was introduced percutaneously into the femoral artery and vein, after which a balloon-tipped thermodilution catheter was advanced through the femoral vein to the pulmonary artery. Before infusion, femoral arterial, pulmonary arterial and pulmonary capillary wedge pressure, as well as cardiac output and coronary sinus blood flow by thermodilution, were measured in triplicate. In addition, blood samples were obtained from the femoral venous and arterial sheaths for measurement of 6-keto $PGF_{1\alpha}$ (the stable metabolite of PGI_2) and plasma renin activity.

PGI_2 infusion: In 10 patients (7 men, 3 women, mean age 52 years), PGI_2 (provided by the Upjohn Company) was infused intravenously after completion of the baseline measurements. Two of these 10 patients had significant 1-vessel, three 2-vessel, and five 3-vessel CAD. Medical therapy, which included beta-adrenergic blocking agents in 9, long-acting nitrate preparations in 6 and calcium antagonists in 6 (Table I), was withheld for 8 hours before the study. The PGI_2 was prepared as a sterile power dissolved in glycine buffer (pH 10.5) and diluted to a concentration of 50 μg/ml. Subsequently, an aliquot of this concentrated solution was added to 250 ml of saline solution, yielding a final concentration of 342 ng/ml. This solution was kept at 2 to 8°C and administered within 2 hours of its preparation. PGI_2 was infused by a microinfusion pump (Harvard Apparatus) through a peripheral venous cannula at incremental doses of 2.5, 5.0, 7.5 and 10 ng/kg/min, each for 15 minutes. At the peak infusion rate, femoral arterial, pulmonary arterial and pulmonary capillary wedge pressure, as well as thermodilution-determined cardiac output and coronary sinus blood flow in triplicate, were again measured, and femoral arterial and venous blood samples were obtained for quantitation of 6-keto $PGF_{1\alpha}$ and plasma renin activity. In 1 patient, the infusion was discontinued after 7.5 ng/kg/min because of atypical chest pain, whereas the remaining 9 patients tolerated 10 ng/kg/min without developing angina. All became flushed during PGI_2 infusion, but no other adverse effects were evident. After the peak infusion rate, the PGI_2 infusion was down-titrated over 15 to 20 minutes.

Glycine buffer (placebo) infusion: In 7 patients (3 men, 4 ministered after baseline measurements. Three had significant 1-vessel, 2 had 2-vessel and 2 had 3-vessel CAD. Of these 7 patients, 2 were taking beta-adrenergic blocking drugs, 6 long-acting nitrates, and 3 calcium antagonists until 8 hours before the study. Glycine buffer (without PGI_2 powder) was added to saline solution, after which its incremental infusion was performed in a manner identical to that just described. No side effects were evident during or after glycine buffer infusion.

Chemical analyses: Because of the short half-life of PGI_2, the plasma concentration of its stable metabolite 6-keto $PGF_{1\alpha}$ was measured.[6] The blood samples for prostaglandin analysis were drawn simultaneously into heparinized plastic syringes and transferred quickly to iced 12-ml tubes containing indomethacin (10 μg) and heparin (1,000 U). They were centrifuged at 2,000 × *g* for 15 minutes at 4°C, and the supernatants were separated and stored at −45°C for subsequent analysis. Plasma 6-keto $PGF_{1\alpha}$ concentrations were measured by the radioimmunoassay method of Dray et al[17] as modified by Campbell et al,[18] as described previously from our laboratory.[19,20] Plasma renin activity was measured by the method of Poulsen and Jorgensen.[21]

Statistical analyses: All values are expressed as mean ± standard deviation. The 2 groups were compared at baseline using Hotelling's T-square analysis.[22] A repeated measures analysis of variance with 1 grouping factor was performed to test for differences between groups and from baseline to peak infusion.[23] When significant interaction was found, Newman-Keul comparisons were made. Otherwise, Duncan's multiple-range test was used to locate significant differences.[23] Linear regression analyses were used to compare both absolute and percent changes in coronary blood flow and coronary vascular resistance from baseline to peak infusion with the changes in mean femoral arterial pressure, diastolic femoral arterial pressure, heart rate–systolic arterial pressure double product, cardiac index and total systemic vascular resistance.[23] A p value <0.05 using a 2-tailed *t* test was considered significant.

Results

Systemic, pulmonary, and coronary hemodynamic alterations: At baseline, the PGI_2 and placebo-treated groups were similar in all respects (Table I). PGI_2 caused an increase in heart rate (from 66 ± 11 to 80 ± 11 beats/min, $p < 0.001$) and cardiac index (from 2.88 ± 0.65 to 3.97 ± 1.17 liters/min/m^2, $p < 0.001$), a decrease in mean femoral arterial pressure (from 96 ± 18 to 86 ± 11 mm Hg, $p < 0.01$) and diastolic femoral arterial pressure (from 69 ± 11 to 61 ± 8, $p < 0.01$), but no change in mean pulmonary arterial pressure (18 ± 4 mm Hg before and after) or capillary wedge pressure (from 10 ± 3 to 11 ± 4 mm Hg, difference not significant [NS]). Double product showed no consistent response and the mean value did not change significantly with PGI_2 (from 8.9 ± 2.2 to 9.7 ± 1.8 × 10^3 U). Both total systemic vascular resistance (from 1,559 ± 550 to 1,040 ± 375 dynes s cm^{-5}, $p < 0.001$) and total pulmonary vascular resistance (from 298 ± 105 to 214 ± 78 dynes s cm^{-5}, $p < 0.001$) decreased. The infusion of placebo produced no significant change in these variables.

PGI_2 caused an increase in coronary sinus blood flow in 7 patients, no change in 1 and a decrease in 2. The mean coronary sinus blood flow did not change significantly (from 100 ± 40 to 121 ± 52 ml/min, NS). Coronary vascular resistance decreased in 9 patients and increased minimally in 1, so that the average coronary

± 0.36 U ($p < 0.001$). In the 7 patients receiving placebo, coronary blood flow increased in 3, decreased in 3 and changed minimally in 1, whereas coronary vascular resistance decreased in 3, increased in 2, and changed minimally in 2. Glycine buffer produced no significant change in either of these variables.

There was a weak correlation between the absolute change in coronary blood flow in response to PGI_2 and the change in both cardiac index ($r = 0.60$, $p = 0.067$) and total systemic vascular resistance ($r = -0.62$, $p = 0.054$), but these relations were not statistically significant. The correlations between the absolute change in coronary blood flow and mean femoral arterial pressure, diastolic femoral arterial pressure and double product did not approach statistical significance. Similarly, the relation between the percentage change in coronary blood flow and the percentage change in any of the aforementioned variables did not approach statistical significance. Finally, there was no correlation between the absolute change or the percentage change in coronary vascular resistance and the absolute or percentage change in the other variables.

Neither double product nor coronary blood flow changed consistently in response to PGI_2, and the correlation between both the absolute and percentage changes in coronary blood flow and double product was not significant. Nevertheless, these 2 variables consistently changed in the same direction.

Serologic alterations: PGI_2 produced a marked increase in 6-keto $PGF_{1\alpha}$ levels in both femoral arterial blood (from 42 ± 29 to 567 ± 216 pg/ml, $p < 0.001$) and venous blood (from 46 ± 31 to 604 ± 229 pg/ml, $p < 0.001$). In contrast, the levels of 6-keto $PGF_{1\alpha}$ in femoral arterial blood (from 14 ± 18 to 13 ± 21 pg/ml, NS) and venous blood (from 14 ± 18 to 17 ± 20 pg/ml, NS) were unaltered in the placebo-treated group (Fig. 1). Conversely, PGI_2 caused no significant change in plasma renin activity (from 0.67 ± 0.57 to 2.07 ± 2.60 ng A_1/ml/h, NS).

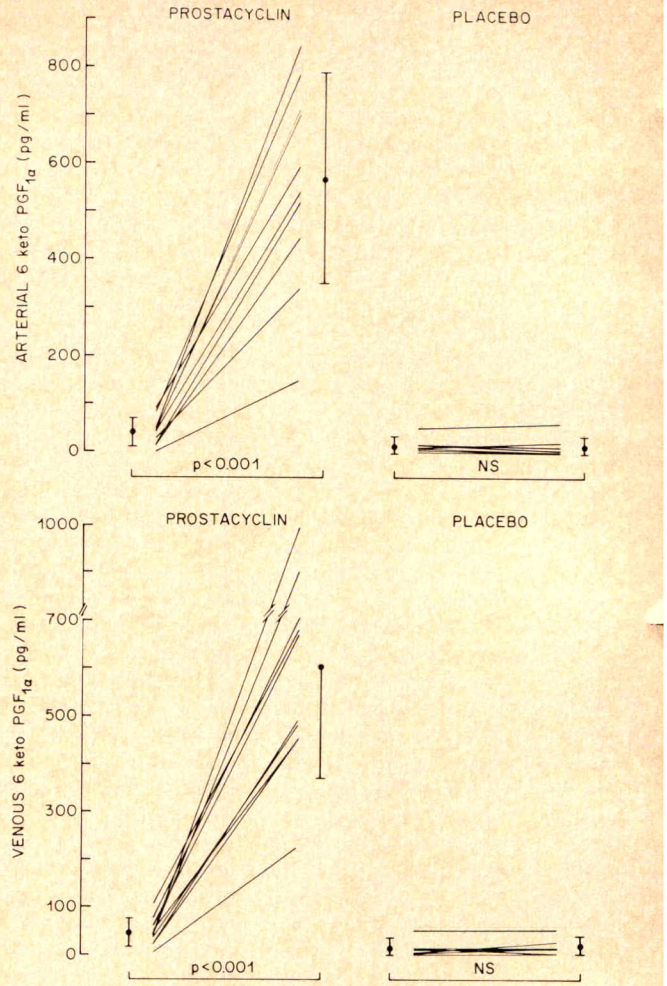

FIGURE 1. Effects of prostacyclin and placebo, respectively, on arterial (**above**) and venous (**below**) 6-keto $PGF_{1\alpha}$ concentrations. Each line represents the data from a single patient, and the means ± 1 standard deviation are shown. Prostacyclin caused a marked increase in both arterial and venous 6-keto $PGF_{1\alpha}$ concentrations.

Discussion

Over the past few years, the infusion of PGI_2 has proved beneficial in patients with congestive heart failure,[9] pulmonary hypertension[10] and arteriosclerotic peripheral vascular disease.[13] Preliminary observations suggest that it may exert a salutary effect in those with angina pectoris at rest.[24] The present study was performed to explore its safety and hemodynamic effects in patients with arteriosclerotic CAD.

Systemic and pulmonary hemodynamic alterations induced by PGI_2: In this study, the intravenous infusion of PGI_2 in patients with CAD and stable angina pectoris produced an increase in heart rate and cardiac index, a decrease in mean and diastolic systemic arterial pressure, and a decrease in total systemic and pulmonary vascular resistance, findings similar to those reported previously in normal persons,[25,26] those with CAD,[27] and those with congestive heart failure.[9] At the same time, PGI_2 induced no consistent change in the double product (an index of myocardial oxygen demand), or pulmonary arterial or pulmonary capillary wedge pressure. Other investigators reported similar findings when the pulmonary capillary wedge and pulmonary arterial pressures were not elevated.[25–27] Thus, the influence of PGI_2 on cardiac output, heart rate, intracardiac filling pressure and vascular resistance in the present study is similar to that reported previously.

Coronary hemodynamic changes caused by PGI_2: In this study, intravenous PGI_2 produced a decrease in coronary vascular resistance ($p < 0.001$) but no significant change in coronary blood flow. In canine models of myocardial ischemia, others[15,16] have noted a dose-dependent decrease in coronary vascular resistance but no change in coronary blood flow with intravenous PGI_2, whereas intracoronary PGI_2 has increased coronary blood flow. Our findings differ from those of Bergman et al,[27] who showed a significant PGI_2-induced increase in coronary blood flow and a decrease in coronary vascular resistance in patients with stable angina. We withheld antianginal medications (including beta-adrenergic blocking agents) for only 8 hours, whereas Bergman et al[27] withheld these agents for 48 hours; therefore, persistent beta-adrenergic blockade in our

patients could explain the difference in coronary blood flow response in our study compared with theirs. In our study, coronary blood flow increased in most patients despite a marked decrease in mean and diastolic systemic arterial pressures, an event that cannot occur in the absence of coronary vasodilatation. In addition, alterations in myocardial oxygen demand (as reflected by double product[28]) probably exerted an effect on coronary blood flow independent of that produced by PGI_2, because PGI_2 caused directionally similar alterations in coronary blood flow and double product. In short, both our study and that of Bergman et al[27] suggest that intravenous PGI_2 produces coronary vasodilatation in patients with CAD.

Although PGI_2 produced a decrease in coronary vascular resistance in patients with CAD, this change may not improve the blood supply to marginally perfused regions of myocardium. In a canine model of myocardial ischemia, Ribeiro et al[29] demonstrated no increase in total flow to ischemic myocardium and no change in the endocardial/epicardial flow ratio in response to PGI_2. Nevertheless, according to these and other investigators,[30,31] PGI_2 diminished the extent of myocardial ischemic injury, possibly through a reduction in the determinants of myocardial oxygen consumption. In patients with CAD and stable angina, 2 recent studies[24,27] reached disparate conclusions about the efficacy of intravenous PGI_2 in preventing pacing-induced ischemia: Bergman et al[27] noted a PGI_2-induced increase in anginal threshold with pacing, whereas Szczeklik et al[24] observed no change. Finally, Szczeklik et al[24] reported a consistent symptomatic improvement with intravenous PGI_2 in patients with recurrent episodes of angina at rest, but Chierchia et al[32] observed symptomatic improvement in only 1 of 9 patients with this clinical syndrome.

Serologic alterations produced by PGI_2: PGI_2 caused a marked increase in plasma 6-keto $PGF_{1\alpha}$ in both arterial and venous blood in comparison with placebo (Fig. 1), an expected finding because 6-keto $PGF_{1\alpha}$ is the major metabolite of PGI_2.[6] The similar levels of 6-keto $PGF_{1\alpha}$ in venous and arterial blood after PGI_2 imply that it (unlike PGE_2) is not degraded by passage through the lungs, an observation noted by others.[3,4] In contradistinction to its effects on plasma 6-keto $PGF_{1\alpha}$ levels, PGI_2 caused no consistent alteration in plasma renin activity.

Clinical implications: Intravenous PGI_2 (to a maximal dose of 10 ng/kg/min) is well tolerated by patients with CAD and stable angina pectoris, producing systemic, pulmonary and coronary vasodilatation, a marked increase in plasma 6-keto $PGF_{1\alpha}$ concentrations and no effect on plasma renin activity. Its therapeutic value in patients with CAD and stable or unstable angina is uncertain and merits further investigation.

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An Improving Prognosis Over Time in Medically Treated Patients With Coronary Artery Disease

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The national mortality rate from coronary heart disease has decreased during the past decade, for reasons that are not yet clear. The mortality rate and the total number of cardiovascular events both decreased during the last 10 years in 1,911 medically treated patients with significant coronary artery disease. This decrease cannot be explained by less sick patients being referred for evaluation. This study suggests that at least part of the decrease in coronary heart disease mortality observed nationally is occurring in patients with established coronary disease. (Am J Cardiol 1983;52:444–448)

Recent reports have described a decrease in mortality from coronary artery disease (CAD) in the United States.[1–11] From 1968 to 1976, unadjusted mortality rates for CAD decreased 12% and the age-adjusted mortality rate decreased 21%.[12,13] The decrease represents a potential annual saving of 191,500 lives nationally.[14]

The cause of the decrease is not clear. It does not appear to be secondary to artifact or changes in the coding of death certificates.[5–7] Fewer people may be developing CAD, which would represent a decrease in incidence. Alternatively, patients with CAD may be living longer. This investigation examines the decreases that occurred over time in cardiovascular mortality and morbidity rates in a consecutive population of patients referred for coronary angiography, and presents evidence that the prognosis has improved for medically treated patients with angiographically documented CAD.

Methods

Patients: Our patient population and information system have been described in detail.[15–18] Briefly, from November 1969 to July 1981, significant CAD (defined as ≥75% luminal diameter obstruction of ≥1 coronary arteries[19]) was diagnosed in 1,911 consecutive medically treated patients with chest pain who were referred to the Duke University Medical Center for cardiac catheterization. Baseline information collected prospectively included multiple descriptors of the history, physical examination, chest roentgenogram, electrocardiogram, and cardiac catheterization. The baseline characteristics used in this study are shown in Table I. They included variables shown by previous analyses[16,17] to be independently associated with future cardiac events, except for arteriovenous oxygen difference, which was not determined during the entire study period. Follow-up information was collected prospectively at 6 months, 1 year, and annually thereafter, and was 99% complete.[16] In our analyses, the follow-up events of interest included both cardiovascular death and total cardiac events (cardiovascular death or nonfatal myocardial infarction). Validation of the accuracy of our follow-up procedures for recognizing nonfatal infarction has been described.[17]

Data analysis: *Decreases over time:* Our purpose was to determine whether fewer cardiovascular deaths and events were occurring over time in our population. We chose 3 methods of investigation. First, we compared the Kaplan-Meier[20] survival and event-free curves for patients seen during 2 study periods (before 1974 and from 1976 to 1979). Second, we determined the 1-year mortality and total cardiac event rates for patients in each year of the study. The estimates of the rates for each year were smoothed by averaging the rates for the particular year with the year before and the year after, since the number of patients seen each year was relatively small. Finally, we used Breslow's formulation[21] of the Cox proportional hazards regression model[22] to determine the association between when a patient entered the study (the year of catheterization) and the likelihood of that patient dying or having a cardiac event.

Controlling for referral bias: Decreases in event rates in our population could be due either to less sick patients being referred for evaluation or to decreases in mortality and events occurring in equally sick patients. The distinction is important if our results are to aid in interpreting the observed national trend. Fewer events occurring in equally sick patients over time implies that an improved case-fatality rate for patients

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TABLE I Baseline Descriptors

Clinical
Age
Sex
Chest pain frequency
Nocturnal chest pain
Progressive chest pain
Preinfarctional chest pain
Variant angina
Congestive heart failure severity
Vascular disease (peripheral or cerebrovascular)
Risk factors (smoking, hyperlipidemia, hypertension, family history, diabetes mellitus)
Previous myocardial infarction (history or electrocardiographic evidence)
Ventricular gallop
Electrocardiogram
Premature ventricular contraction
Left bundle branch block
Nonspecific intraventricular conduction defect (QRS duration ≥0.12 second without left or right bundle branch block)
ST-T-wave changes
Chest roentgenogram
Cardiomegaly
Cardiac catheterization
Left ventricular performance
Contractility (normal, diffusely abnormal)
Anterior, apical, or inferior asynergy
Left ventricular end-diastolic pressure
Mitral insufficiency
Anatomy
Number of diseased vessels
Significant left main, left anterior descending, left circumflex, or right coronary artery lesions

with CAD is partly responsible for the national decrease. This conclusion could not be justified if the decrease in event rates in our population was due to changes in referral practices.

We chose to examine this issue in 2 ways. First, we determined whether changes in the population mix (as assessed by the baseline characteristics) had occurred that would affect the risk of mortality or a cardiac event. Second, we determined whether significant decreases in event rates were still present after we adjusated for changes in the population mix.

Changes in the population mix: Spearman's rank correlation was used to determine whether the prevalence of any of the baseline characteristics at the time of catheterization had increased or decreased over time. Not all characteristics affect how likely a patient is to have a cardiac event. In addition, the importance in predicting prognostic events among the characteristics varies. We previously analyzed 81 separate baseline characteristics[15–18] in this population to determine which variables are independently associated with future events (either cardiovascular death or total cardiac events). These variables are included among the baseline descriptors noted in Table I. We summarized the combined effect on mortality or total cardiac events of all the variables by a "hazard score" (see Appendix for details). The hazard score summarizes in 1 variable the net mortality risk for a patient based on all the important descriptors known about that patient at the time of referral for evaluation. One measure of assessing whether less sick patients were being referred over time was to determine whether the hazard score had changed significantly over time. This was done using the Spearman correlation coefficient.

Independent (adjusted) changes in event rates over time: To determine the independent effect on future events of when a patient was referred for catheterization, we repeated the Cox analyses described earlier, including the baseline descriptors noted in Table I as covariates or confounding factors.[16] The results of this analysis revealed whether significant decreases in mortality or total cardiac events occurred over time after controlling for any known changes in the population mix.

We were particularly concerned that the recent availability of cardiac catheterization and aortocoronary bypass surgery at the beginning of the study period may have introduced a backlog of substantially different patients. This was suggested by a longer duration of symptoms for patients referred during the first year. Although previous analyses[16,17] have shown no independent effect of the duration of a patient's symptoms on future events, we were concerned that some unrecognized, prognostically important variables may have been present in these patients. Therefore, we repeated the Cox analyses excluding patients seen before July 1971. The analyses quantitated the trends present in the 1,807 consecutive medically managed patients who were catheterized from July 1971 to July 1981.

The magnitude of the decrease: We estimated the magnitude of the decreases by calculating the ratio of the estimated 1-year mortality and event rates in 1978 and 1971. The magnitude of the decrease after adjusting for any population differences was obtained from the adjusted Cox analyses (see previously). The relative risk of mortality and the relative risk of having a cardiovascular event for patients entering the study population in 1978 compared with those entering in 1971 were estimated from the ratio of the hazard functions for these 2 times of entry into the study. The ratios of the hazard functions were also calculated using the results of the analyses that excluded the first 1.5 years of data.

Results

In the follow-up to date, 530 patients have had cardiac events and 383 cardiovascular deaths have occurred. If only patients catheterized after July 1971 are considered, 472 patients have had cardiac events, including 338 cardiovascular deaths.

Decreases over time: Figures 1 and 2 show the Kaplan-Meier empirical survival and event-free curves for all patients evaluated from 1970 to 1973 and from 1976 to 1979. At all times during the follow-up period, fewer deaths and cardiovascular events have occurred in patients seen later than in those seen earlier. Figure 3

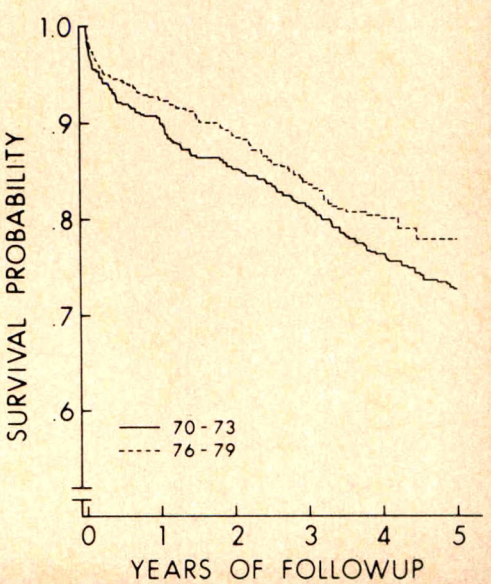

FIGURE 1. Survival probability (Kaplan-Meier) for patients first evaluated for different time periods.

shows the estimated 1-year mortality and total cardiac event rates as a function of each successive year of entry. Mortality and total cardiac events have progressively decreased during the study period.

Changes in the population mix over time: Table II illustrates the changes over time in the prevalences of the baseline characteristics. Although the prevalences of many of the baseline characteristics at the time of catheterization had changed significantly ($p < 0.05$), the individual changes were small. Some changes tended to increase the risk and others tended to decrease it, counterbalancing the effect on mortality. While statistically significant changes occurred, their clinical importance for prognosis was negligible. The significant changes themselves should be viewed with some skepticism because of the multiple number of comparisons performed. If the 37 characteristics were independent of each other, 2 significant ($p < 0.05$) changes would be expected by chance alone. The overall net risk, or hazard score, did not change significantly over time ($p = 0.34$).

Independent (adjusted) changes in event rates over time: The preceding analyses demonstrate significant decreases in event rates that are not explained by changes in the population mix. We would expect, then, that independent decreases in event rates had occurred over time in our population. The results of the Cox analysis (Table III) support this conclusion. Significant decreases in mortality and total cardiac events are present before and after controlling for baseline differences in the population over time. Decreasing trends in mortality and total events were also present, although less significant, when only patients seen after July 1971 are included.

The magnitude of the decrease: The estimated 1-year mortality rate in 1971 was 9.75% and the estimated 1-year cardiac event rate was 15.58% (Fig. 3). In 1978, the corresponding rates were 7.84% and 13.28%. For a patient first seen in 1978, the 1-year risk of dying was 80% of that for a patient evaluated in 1971. The 1-year risk of having any cardiac event for patients evaluated in 1978 was 85% of the risk for patients evaluated in 1971. The magnitude of the decreases estimated from the adjusted Cox analyses were similar: a relative hazard ratio for patients entering in 1978 compared with 1971 of 0.66 for mortality and 0.71 for total events (95% confidence intervals 0.47, 0.94 and 0.54, 0.94, respectively). When the adjusted trends excluding the first 1.5 years of data were used, the relative hazard ratio for patients entering in 1979 compared with 1972 was 0.67 for mortality and 0.75 for total events (95% confidence intervals 0.45, 1.00 and 0.55, 1.04, respectively).

Discussion

This study documents a decrease in both mortality and total cardiac event rates over the past decade in a patient population with well-characterized CAD. The decrease does not appear to be due to less sick patients being referred for evaluation. Decreases are present even after adjusting for the slight changes in baseline characteristics that occurred during this period and excluding the early patients from the analyses. Thus, the decrease is not attributable to a patient selection bias, with the sicker patients being referred for surgery. Our findings suggest that at least part of the national decrease in CAD mortality results from an improved survival for patients with CAD. This does not preclude a concurrent decrease in the incidence of CAD. We could not examine this hypothesis.

The magnitude of the decrease reported nationally reflects age-adjusted mortality rates in the entire United States population. The magnitude of the decrease estimated in our population includes only patients with documented CAD. These are not comparable. No attempt has been made to estimate how much of the national decrease may be a result of patients with established CAD living longer. The significance of our findings is limited to showing, in our population, that patients with established CAD are living longer and having fewer events.

Previous reports of changes in survival patterns over time have not included detailed information on the extent or severity of CAD. Our findings support reports from Rochester, Minnesota, based on comprehensive

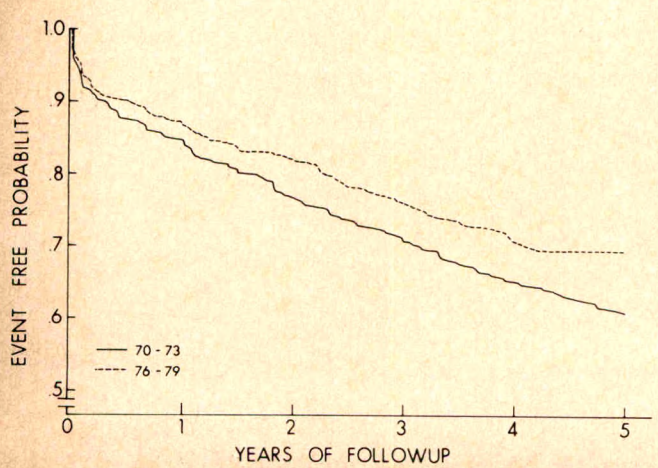

FIGURE 2. Total cardiac event-free probabilities (Kaplan-Meier) for patients first evaluated for different time periods.

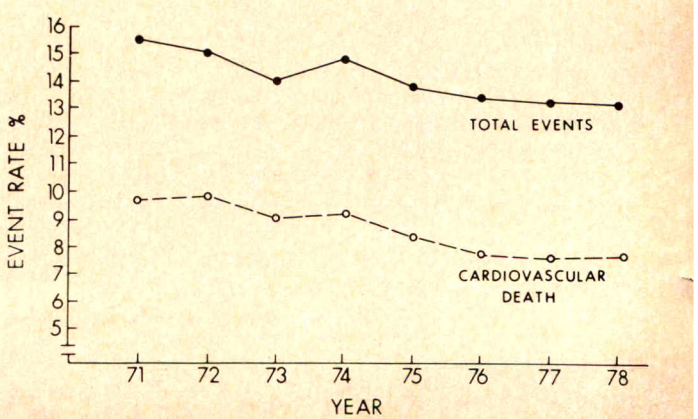

FIGURE 3. Changes in prognosis over time—estimated 1-year event rates.

TABLE II Changes* in the Prevalences of Baseline Characteristics Over Time

Increased	No Change	Decrease
Age (0.11)	Progressive chest pain (−0.004)	Males (−0.06)
History of smoking (0.08)	Preinfarction chest pain (−0.01)	Nocturnal chest pain (−0.16)
History of hypertension (0.10)	Variant angina (0.01)	Chest pain frequency (−0.07)
Family history (0.11)	Congestive heart failure (class IV) (−0.03)	Hyperlipidemia (−0.08)
History of MI (0.07)	Peripheral vascular disease (0.04)	Systolic blood pressure (−0.16)
ST-T-wave changes (0.13)	Cerebral vascular disease (0.04)	Ventricular gallop (−0.05)
Anterior LV asynergy (0.17)	History of diabetes mellitus (0.04)	ECG PVCs (−0.06)
Apical LV asynergy (0.17)	ECG Q waves (0.03)	ECG LBBB (−0.07)
Inferior LV asynergy (0.14)	ECG intraventricular conduction defect (0.04)	Normal contractility (−0.08)
LVEDP (0.11)	Cardiomegaly (−0.01)	Number of diseased vessels (−0.16)
Mitral insufficiency (0.09)	Diffusely abnormal contractility (−0.02)	Significant left main stenosis (−0.10)
	Significant RCA stenosis (0.01)	Significant left circumflex stenosis (−0.08)
	Hazard score or overall net risk (−0.02)	Significant left anterior descending stenosis (−0.07)

* Changes = Spearman correlation $p < 0.05$.
Spearman correlation coefficients shown in parenthesis.
ECG = electrocardiographic; LBBB = left bundle branch block; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; PVC = premature ventricular contraction; RCA = right coronary artery.

TABLE III Changing Prognosis Over Time (Cox Model Statistics* Unadjusted and Adjusted Decreases)

Analysis	Outcome†	
	Survival	Total Events
All patients		
Unadjusted	6.47 (0.011)	11.93 (<0.001)
Adjusted‡	5.18 (0.023)	5.84 (0.016)
Patient entering after 7/1/71		
Unadjusted	3.57 (0.059)	6.98 (0.008)
Adjusted‡	3.77 (0.052)	3.00 (0.083)

* All values are expressed as chi squares (1 degree of freedom) with corresponding p values measuring the association between when a patient was referred for evaluation and future events.
† The dependent variable for survival was the time until a cardiovascular death. Total events refers to the time until a cardiovascular death or nonfatal myocardial infarction.
‡ Adjusted refers to inclusion of baseline descriptors in Table I as covariates (see text).

community health records that demonstrated a decrease in both incidence and case-fatality rates.[23,24] The magnitude of the decrease they reported in 1-year mortality (50%) from 1965 to 1975 in patients with clinically evident CAD appears to be similar to our own, although without invasive characterization it is difficult to compare the 2 populations. A report from a large prepaid health plan[25] revealed that from 1971 to 1977, the number of persons hospitalized for acute myocardial infarction decreased, but the proportion of deaths among those admitted did not change. The author of that report characterized his finding as a decrease in incidence with no change in the case-fatality rate. A "case" in that study however, referred to acute myocardial infarction rather than angiographically defined disease. In addition, the follow-up period was limited to the period of hospitalization. Long-term follow-up study might have revealed improved survival for patients discharged after acute myocardial infarction, as suggested by many of the beta-blocker trials.[26,27]

Because most patients with CAD live, the reduction in risk for an individual patient in a given year is quite small despite the apparent magnitude of the decrease. For example, if a patient seen in 1971 has an 8% risk of dying in 1 year, a similar patient seen in 1978 might have only a 6.4% risk of dying (80% of 8%), or a change per year of <1% (1.6% decrease in 7 years).

Our analyses demonstrate a method for controlling for selection bias introduced by changes in a population over time. Any investigation designed to determine whether a change in outcome in a population has occurred should address the issue of whether the change is due to a selection bias of which patients are enrolled. The Cox model analysis that adjusts for the covariates that affect the outcome event of interest is a powerful technique capable of identifying changes in outcome that may be due to the combined effect of relatively small changes in individual characteristics.[28,29] Other investigators may wish to use a similar technique to control for possible selection bias introduced by changes in their patient population over time.

We attempted to control for prognostically important sources of bias that might have been present in our population over time. We were particularly concerned that the recent availability of cardiac catheterization and aortocoronary bypass surgery at the start of our data collection may have initially introduced a backlog of substantially different patients. For that reason, we analyzed our results a second time, excluding the first 1.5 years of data and examining the adjusted trends in our population from mid-1971 through 1981. Because the ability of Cox analyses to detect changes is dependent in part on the number of events that occur and the length of follow-up, we would expect the significance of the analyses excluding the first 1.5 years of data to decrease. Decreasing trends (although not always significant at the 0.05 level) were still present in mortality and total cardiac events. Although reassuring, these results cannot exclude the possibility that an unrecognized source of chronology bias[30] existing beyond this period may have influenced our results.

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Appendix

Using the hazard score to summarize mortality risk: The mortality risk for a patient can be represented by a "hazard score." The hazard score summarizes in 1 variable the net contribution of all prognostically important baseline descriptors to the mortality risk for a patient. Using Breslow's formulation[21] of the Cox proportional hazards regression model,[22] and including all pertinent baseline descriptors as covariates or confounding factors,[16] the independent contribution to survival of each of the baseline descriptors can be quantitated. The hazard score is then calculated as: $B_1 X_1 + B_2 X_2 + \ldots B_n X_n$, where $X_1, \ldots, X_n$ = the baseline descriptors and $B_1, \ldots, B_n$ = their corresponding Cox regression coefficients. At any particular time t, the predicted survival S(t) can be calculated as $S(t) = S_0(t)^{\exp h}$, where $S_0(t)$ = the estimated survival probability with all variables set equal to their means and h = the hazard score.

Directional ST-Segment Deviation in Graded Exercise Tests Correlated With Motion of the Individual Segments of the Left Ventricular Wall

JAMES N. KARNEGIS, MD, PhD, JOHN MATTS, PhD, NAIP TUNA, MD, PhD, KURT AMPLATZ, MD, RICHARD B. MOORE, MD, HENRY BUCHWALD, MD, PhD, and the POSCH* Group

An exercise test may be characterized as positive because of the production of either electrocardiographic ST-segment depression or elevation. The relationship of exercise-induced ST-segment deviation to the specific motion abnormalities of the individual segments of the left ventricular wall was investigated. The first 280 subjects to enter the Program of Surgical Control of Hyperlipidemia were studied by treadmill exercise testing and left ventriculography. The results showed that exercise-induced ST-segment elevation could occur without evidence in the resting subject of either dyskinesia or aneurysm of the left ventricle, that the area of left ventricular damage was much greater in subjects with exercise-induced ST-segment elevation than in those with ST-segment depression, and that wall motion abnormalities were concentrated in the inferoposterior area in the group with ST-segment elevation, but were generally scattered throughout the left ventricular wall in the group with ST-segment depression.

(Am J Cardiol 1983;52:449–452)

A positive exercise test is generally considered to indicate the presence of myocardial ischemia. The interpretation that the test is positive chiefly depends on recording at least a minimal specified deviation of the ST segment of the electrocardiogram (ECG) during or immediately after exercise, compared with the position of the ST segment on the control tracing. Although the positive test is usually characterized by depression of the ST segment with exercise, in some persons it may become elevated instead. An exercise-induced elevated ST segment may possibly be associated with a left ventricular (LV) aneurysm or dyskinetic area,[1] but little is known about the specific abnormalities of motion of the individual LV segments and their relation to directional changes of the ST segment. Therefore, we analyzed LV segmental wall motion in subjects in the Program of Surgical Control of Hyperlipidemia (POSCH) who developed either ST-segment elevation or depression during a graded treadmill exercise test.

Methods

POSCH is a study of the effect of reducing the level of blood lipids on the natural history of the atherosclerotic disease process in hyperlipidemic subjects. Partial ileal bypass has been used in the management of hyperlipidemia since 1962; this procedure is the modality of intervention in the treatment group because it provides maximal reduction in blood lipid levels.

POSCH subjects at the time of entry into this secondary intervention clinical trial were 30 to 64 years of age, with 1 myocardial infarction documented by enzymatic and electrocardiographic criteria, a blood cholesterol level of ≥220 mg/dl, a systemic arterial pressure of <180/105 mm Hg, no other cardiac disease, and no other serious illness. The protocol excluded from the study subjects with a LV aneurysm detectable on physical examination or thoracic roentgenography. Baseline evaluation included selective cine left ventriculography and a graded exercise test. The LV wall in the right anterior oblique view was divided from the superior aspect clockwise into 3 anterolateral segments (numbered 1 through 3) and 3 inferoposterior segments (numbered 4 through 6) (Fig. 1). The movement of each segment was recorded as normal (normal inward movement of the various segments of the LV wall in systole), hypokinetic (reduced inward movement of the segments in LV systole), akinetic (no systolic movement of the segments) or dyskinetic (outward movement of segments in LV systole). A LV aneurysm was defined as a circumscribed dilatation or bulge in both ventricular systole and diastole. The ejection fraction was also calculated from the left ventriculogram.

The graded exercise test used the Bruce protocol modified by the addition of a 3-minute stage 0 (1.7 mph, 0% grade). Subjects were exercised until symptom- or sign-limited. A positive test was defined as an exercise-induced ≥1 mm depression or elevation in the ST segment of any lead in the electrocardiogram 80 ms after the J point compared with the proceeding PR segment in ≥3 consecutive beats. The ST segment may be isoelectric, elevated or depressed in relation to the PR segment as recorded on the control tracing before

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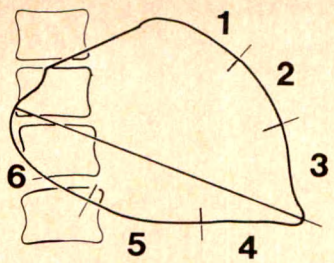

FIGURE 1. The left ventricle in the right anterior oblique (RAO) view. The wall of the left ventricle is divided from its superior aspect clockwise into 3 anterolateral segments (1 through 3) and 3 inferoposterior segments (4 through 6).

exercise. In this research project, a 15-lead ECG (leads I, II, III, CS_5, aVL, aVF, V_1 through V_6, X, Y and Z) was recorded before and during recovery from exercise, and a 9-lead ECG (leads CS_5, aVL, aVF, V_4 through V_6, X, Y, and Z) was recorded during exercise. Lead CS_5 is a bipolar recording from the V_5 and right arm electrodes.

Statistical significance between the ST-depressed and the ST-elevated groups with respect to abnormal and normal numbers was assessed using Fisher's exact test for 2 × 2 tables. The International Mathematics and Statistical Library subroutine on the University of Minnesota Cyber 730 was used. The p values are the probability of achieving a 2 × 2 table as extreme or more extreme than the observed data.

For the difference in medians the 2 groups were divided into the number in each group with a value less than or equal to the population median and the number with a value greater than the population median. These data were placed in a 2 × 2 table and tested by Fisher's exact test as just described.

Results

We report here the baseline data from the first 280 subjects to enter POSCH. Of these, 127 (45%) had a positive graded exercise test as defined herein, 116 with a depressed and 11 with an elevated ST segment. Fifty percent (58 of 116) of those who developed ST-segment depression with exercise and 100% (11 of 11) of those who showed exercise-induced ST-segment elevation had abnormal Q/QS patterns according to the Minnesota Code for resting electrocardiograms.[2] The abnormal Q/QS pattern was located in the anteroseptal area of the heart in 36% (42 of 116) of the ST-depressed group and in 91% (10 of 11) of the ST-elevated group. The Q/QS abnormality in the remaining subject of the ST-elevated group was recorded in the inferoposterior area. In the ST-elevated group, 9 of the 10 subjects with abnormal anteroseptal Q/QS patterns showed some elevation of the ST segment on the resting ECG in the same lead showing the Q/QS abnormality; in the remaining case and in the subject with an abnormal Q/QS pattern in the inferoposterior area, the ST segment was isoelectric on the resting tracing. Of the subjects who had an abnormal Q/QS pattern in the anteroseptal area on the resting ECG and who also developed ST-segment deviation with exercise, 19% (10 of 52) showed ST-segment elevation and 81% (42 of 52) showed ST-segment depression. Four of the 11 who had exercise-induced ST-segment elevation simultaneously developed ST-segment depression in other leads.

TABLE I Total Number of Left Ventricular Segmental Wall Motion Abnormalities by Direction of Exercise-Induced ST-Segment Deviation

Abnormal LV Segments (n)	ST-Segment Depression		ST-Segment Elevation	
	n	%	n	%
0	42	36.2	0	0.0
1	21	18.1	1	9.1
2	32	27.6	3	27.3
3	11	9.5	2	18.2
4	7	6.0	4	36.4
5	0	0.0	1	9.1
6	3	2.6	0	0.0
Total	116	100	11	100
Median (p <0.004)	1		3	

LV = left ventricular.

TABLE II Percent of Individual Left Ventricular Segments With Motion Abnormalities by Direction of Exercise-Induced ST-Segment Deviation

LV Segment	ST-Segment Depression (n = 116)	ST-Segment Elevation (n = 11)	p
Anterolateral 1	23.5	0.0%	NS
Anterolateral 2	5.3	9.1%	NS
Anterolateral 3	17.7	54.5%	<0.01
Inferoposterior 4	22.1	81.8%	<0.001
Inferoposterior 5	24.8	81.8%	<0.001
Inferoposterior 6	38.9	63.6%	NS

LV = left ventricular; NS = not significant.

On left ventriculography none of the 127 subjects showed an aneurysm and none showed dyskinesia of the LV wall. LV segmental wall motion abnormalities were limited to hypokinesia or akinesia, or both. Table I summarizes the distribution of the total number of LV segmental wall motion abnormalities in both the ST-depressed and the ST-elevated positive graded exercise test subjects. Thirty-six percent of the ST-depressed group but none of the ST-elevated group had normal contraction of all 6 LV segments. The median number of LV segments with abnormal motion was 1 for the ST-depressed group and 3 for the ST-elevated group (p <0.004).

Table II shows the percent of the ST-depressed and ST-elevated groups who displayed abnormality of motion in each of the 6 segments of the left ventricular wall. Anterolateral segment 2 was infrequently involved in either group. Of the remaining segments, LV segmental wall motion abnormalities were roughly equally distributed in the ST-depressed group, but clustered in the inferoposterior area in the ST-elevated group. The difference between the 2 groups was statistically significant (p <0.01) for segment 3 and very highly significant (p <0.001) for segments 4 and 5.

The ECG lead in which the positive test with the greatest ST-segment shift was recorded is listed for both groups in Table III. Bipolar chest lead CS_5 and lead V_4 accounted for most of the positive recordings in both the ST-depressed and the ST-elevated group. Lead CS_5 was

TABLE III Electrocardiographic Leads Showing Exercise-Induced ST-Segment Deviation: Positive Graded Exercise Test Group

	ST-Segment Depression		St-Segment Elevation	
ECG Lead	n	%	n	%
CS_5	72	62	2	18
V_4	15	13	8	73
V_5	10	9	...	...
aVF	9	8	...	...
V_6	6	5	...	...
Others (V_2,X,Y,III)	4	3	1	9
Total	116	100	11	100

TABLE IV Percent of Electrocardiogram Leads Positive for Graded Exercise Test by Motion Abnormalities of Individual Left Ventricular Segments

	Left Ventricular Segment					
Positive Graded Exercise Test ST-Segment Depression	1	2	3	4	5	6
Percent of subjects diagnosed from lead V_4 (n = 15)	40	13	13	20	27	40
Percent of subjects diagnosed from lead CS_5 (n = 72)	19	1	12	18	21	39

TABLE V Percent of Electrocardiogram Leads Positive for Graded Exercise Test by Motion Abnormalities of Individual Left Ventricular Segments

	Left Ventricular Segment					
Positive Graded Exercise Test ST-Segment Elevation	1	2	3	4	5	6
Percent of subjects diagnosed from lead V_4 (n = 8)	0	12	62	100	100	50
Percent of subjects diagnosed from lead CS_5 (n = 2)	0	0	0	50	50	100

the positive lead in 62% and lead V_4 in 13% of the ST-depressed group, whereas lead CS_5 was the positive lead for 18% and lead V_4 for 73% of the ST-elevated group.

Table IV shows, for the ST-depressed group, the percent of those whose test was interpreted as positive according to either lead V_4 or lead CS_5 and who showed motion abnormalities in the individual segments of the LV wall. Neither lead V_4 nor lead CS_5 indicated predictably motion abnormalities of the various LV segments.

Table V shows for the ST-elevated group the percent of those whose test was interpreted as positive according to either lead V_4 or lead CS_5 and who showed individual LV segmental wall motion abnormalities. All 8 of the positive cases judged by lead V_4 had abnormal motion of segments 4 and 5, and 5 and 4 of these 8 cases also showed abnormal motion of segments 3 and 6, respectively. Both of the positive cases according to lead CS_5 had abnormal motion of segment 6, with each showing additional involvement of either segment 4 or 5.

Discussion

The appearance of ≥1 mm of elevation in the ST segment during or immediately after exercise is relatively infrequent. In the first 280 POSCH subjects, exercise-induced ST-segment elevation occurred in 11 (3.9%). Chahine et al[3] reported a similar figure of 3.5%. The frequency of exercise-induced ST-segment elevation may be expected to depend, among other things, on the composition of the population studied.[4]

ST-segment elevation with exercise may be related to several factors, including a discrete LV aneurysm,[3] aneurysmal bulging in an area of localized myocardial ischemia,[1] severe ischemic cardiac disease,[5,6] and Prinzmetal's variant angina.[7]

ST-segment elevation with exercise is reported to be variably associated with a LV aneurysm. When studied by cardiac fluoroscopy in 1 reported series, an aneurysm was present in 33% of patients with exercise-induced ST-segment elevation,[8] and in another study of such patients, left ventriculography demonstrated a LV aneurysm in 86%.[3] In contrast, none of our subjects had an aneurysm on left ventriculography, which was not surprising because the protocol excluded from the study subjects with evidence of a LV aneurysm or its sequelae, as already described herein. Evidently, the screening process had effectively eliminated such subjects. The LV segmental wall motion abnormalities in our subjects were limited to hypokinesia or akinesia. In particular, none of those who developed ST-segment elevation with exercise showed dyskinesia of any of the various segments of the LV wall as judged by left ventriculography performed with the subject at rest. Although this finding does not support the concept that exercise-induced ST-segment elevation is related to left ventricular dyskinesia, it clearly does not exclude it because transient dyskinetic areas could possibly develop during the period of exercise.

Both the number of LV segments showing abnormal wall motion and their distribution differed in subjects with exercise-induced ST-segment elevation compared with those with ST-segment depression (Tables I and II). LV damage was greater in the group with ST-segment elevation and was mostly concentrated in the inferoposterior area, whereas the abnormal segments showed no particular localized distribution in the group with ST-segment depression. The number of abnormal segments correlated with the ejection fraction, the details and analysis of which will be reported separately.

Exercise-induced ST-segment elevation was not a necessary consequence of an abnormal Q/QS pattern because the latter was present in half of those who developed ST-segment depression with exercise. Similarly, the presence of an abnormal Q/QS pattern located specifically in the anteroseptal area was not a determinant in the development of ST-segment elevation with exercise because 81% of cases with these 2 features showed exercise-induced ST-segment depression.

The observation of LV segmental wall motion abnormalities in the inferoposterior area of the left ventricle in our subjects who had electrocardiographic ev-

idence of anteroseptal myocardial damage and who developed ST-segment elevation with exercise indicates that these subjects had widespread and severe coronary occlusive disease and is consistent with the data of Cabin and Roberts.[9] These investigators, in a quantitative analysis of coronary arterial disease in patients with healed myocardial infarction, found that of those who had had an anterior myocardial infarction, 95% had severe narrowing (76 to 100%) of >1 coronary artery and 50 and 95%, respectively, had severe narrowing of the left circumflex and right coronary arteries.

The predominant electrocardiographic lead detecting the greatest exercise-induced ST-segment elevation was lead V_4 and, to a much lesser extent, lead CS_5 (Table III). These frequencies were reversed in the ST-depressed, with lead CS_5 and, to a lesser extent, lead V_4 most commonly showing the greatest exercise-induced ST-segment depression. Leads V_4 and CS_5 correlated with inferoposterior myocardial damage in the ST-elevated group (Table V) but did not help in localizing LV segmental wall motion abnormalities in the ST-depressed group (Table IV).

Thirty-six percent of the group that developed ST-segment elevation during exercise showed a simultaneous depression in the ST segment in another lead. This finding suggests that exercise-induced ST-segment elevation may, at least in part, be a reciprocal electrical phenomenon, but it is probably also in some manner related to the large area of myocardial damage, as evidenced by the wall motion abnormalities concentrated in the inferoposterior portion of the left ventricle.

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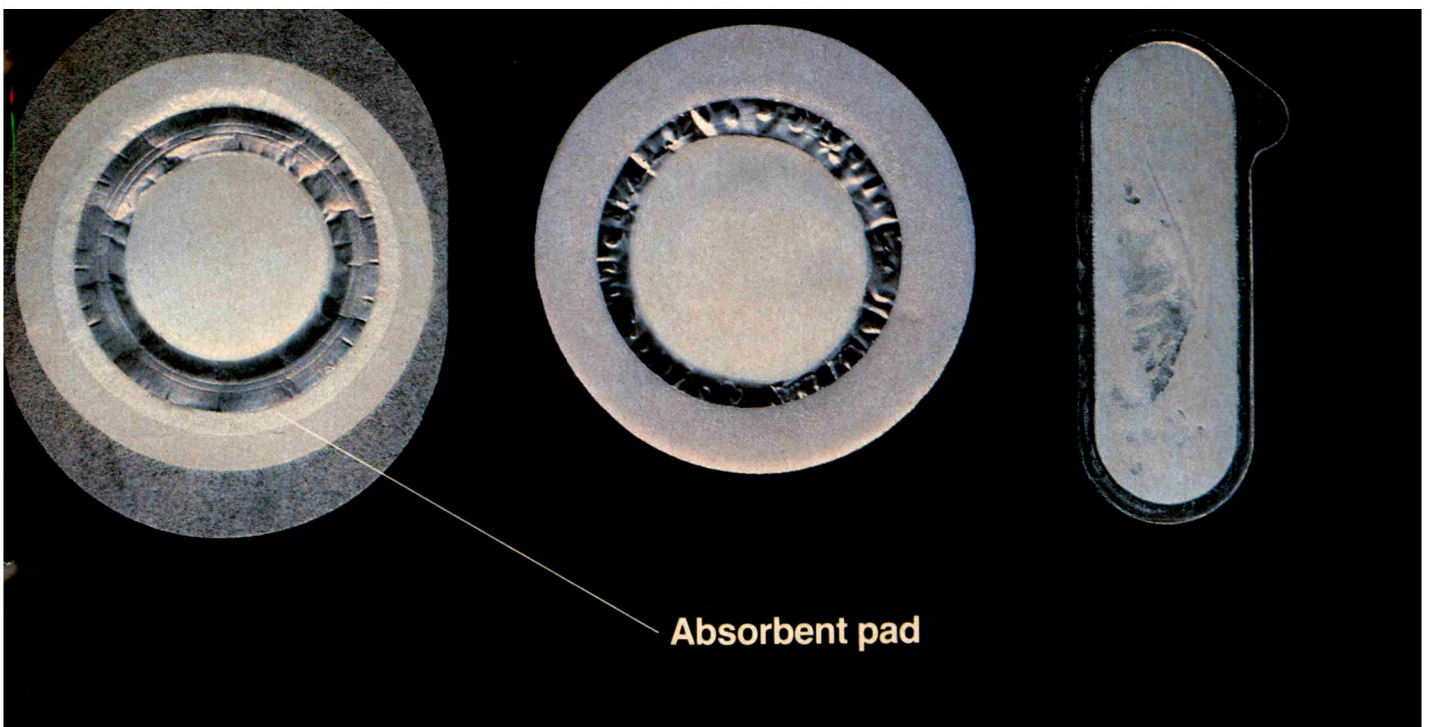

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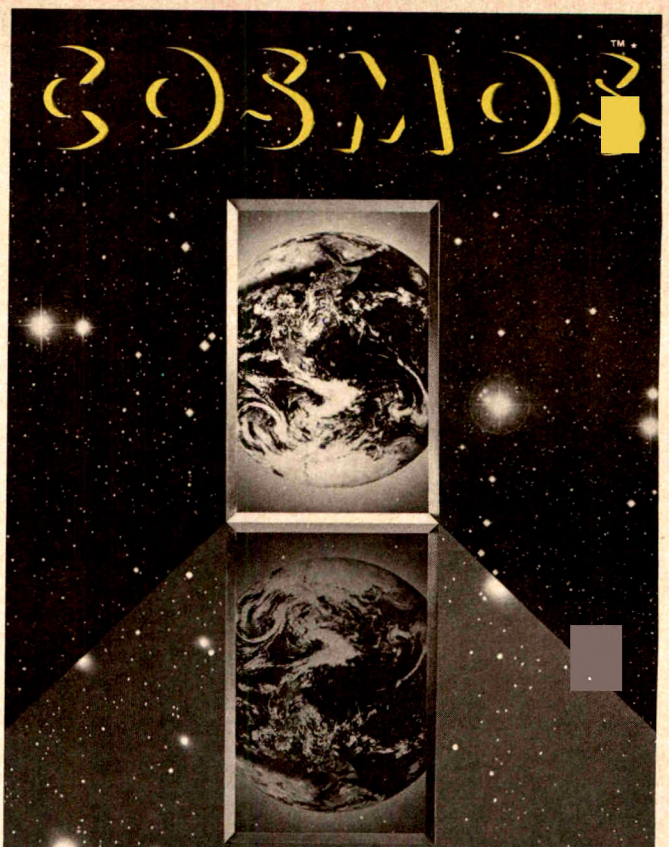

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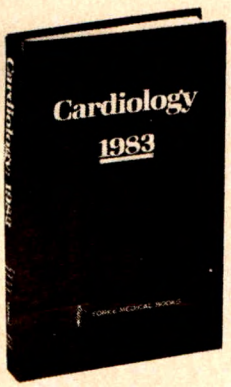

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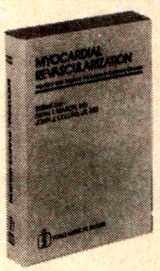

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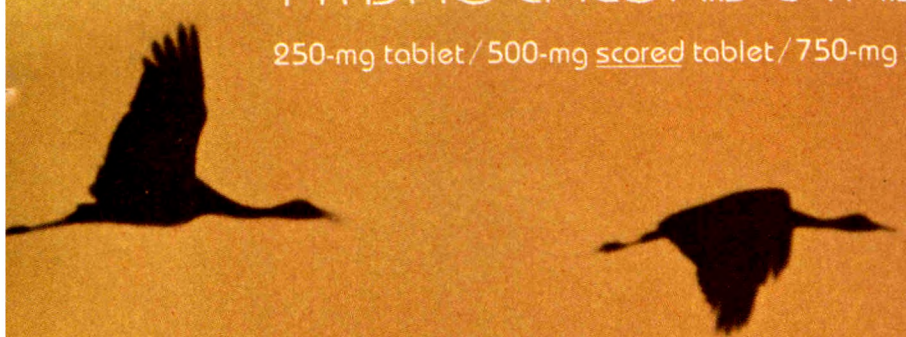

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A Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: General —During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

Routine blood counts are advisable during maintenance procainamide therapy.

ADVERSE REACTIONS: Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS).

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride) tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dose of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dose of 0.5 to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

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Procan SR 750 mg (orange, scored, film-coated tablet. P-D 205) is available in bottles of 100 (N 0071-0205-24) and in unit-dose packages of 100 (10 strips of 10 tablets each) (N 0071-0205-40). Each sustained-release tablet contains 750 mg procainamide hydrochloride.

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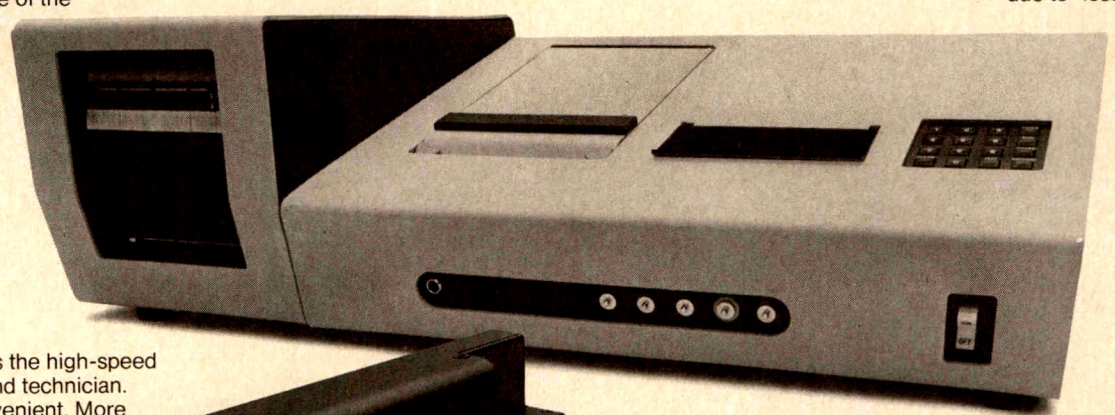

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[1] **Presented at the ambulatory monitoring workshop, American College of Cardiology, Atlanta, GA, April, 1982, H. L. Kennedy, M.D. investigator.**

Also, *Circulation*, Vol. 66, October, 1982, Page II-72.

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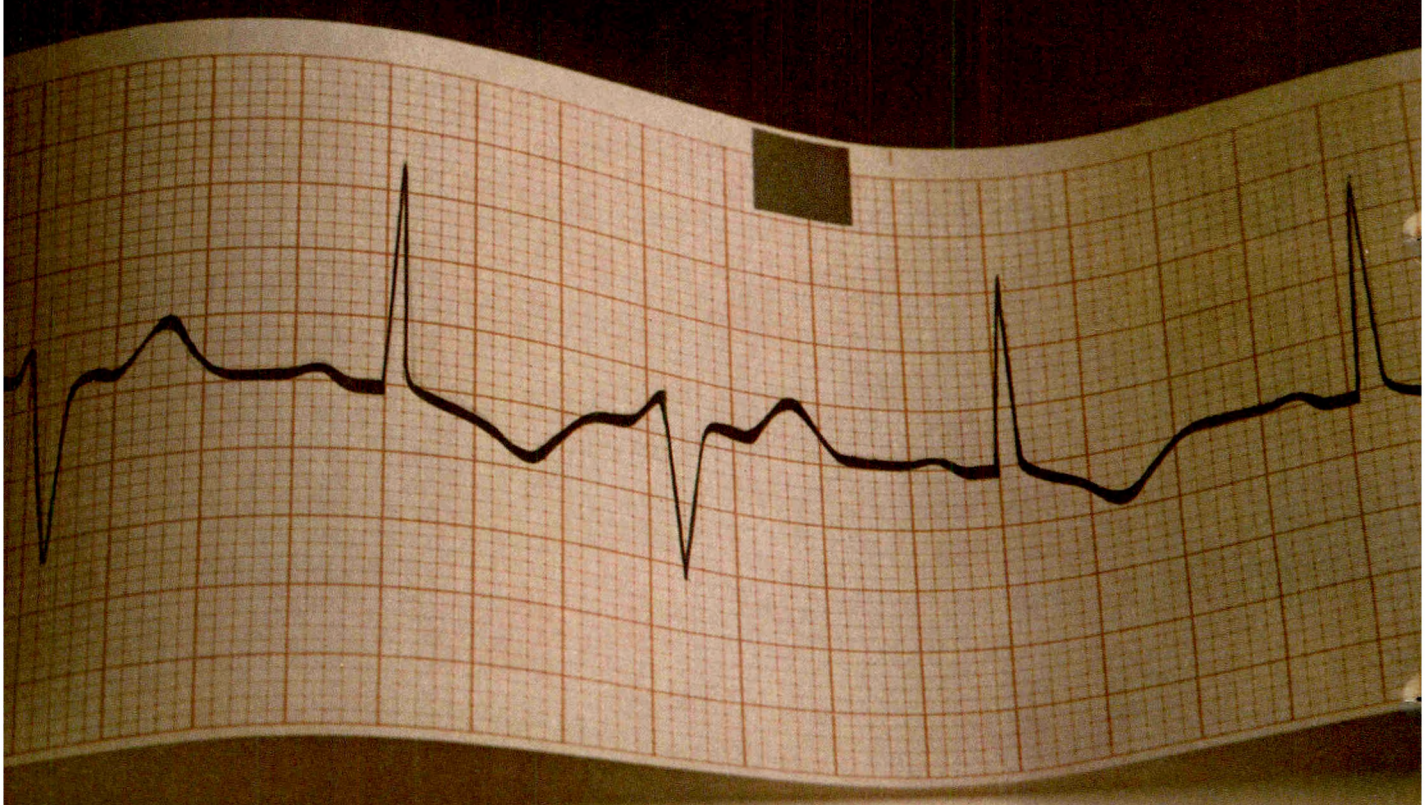

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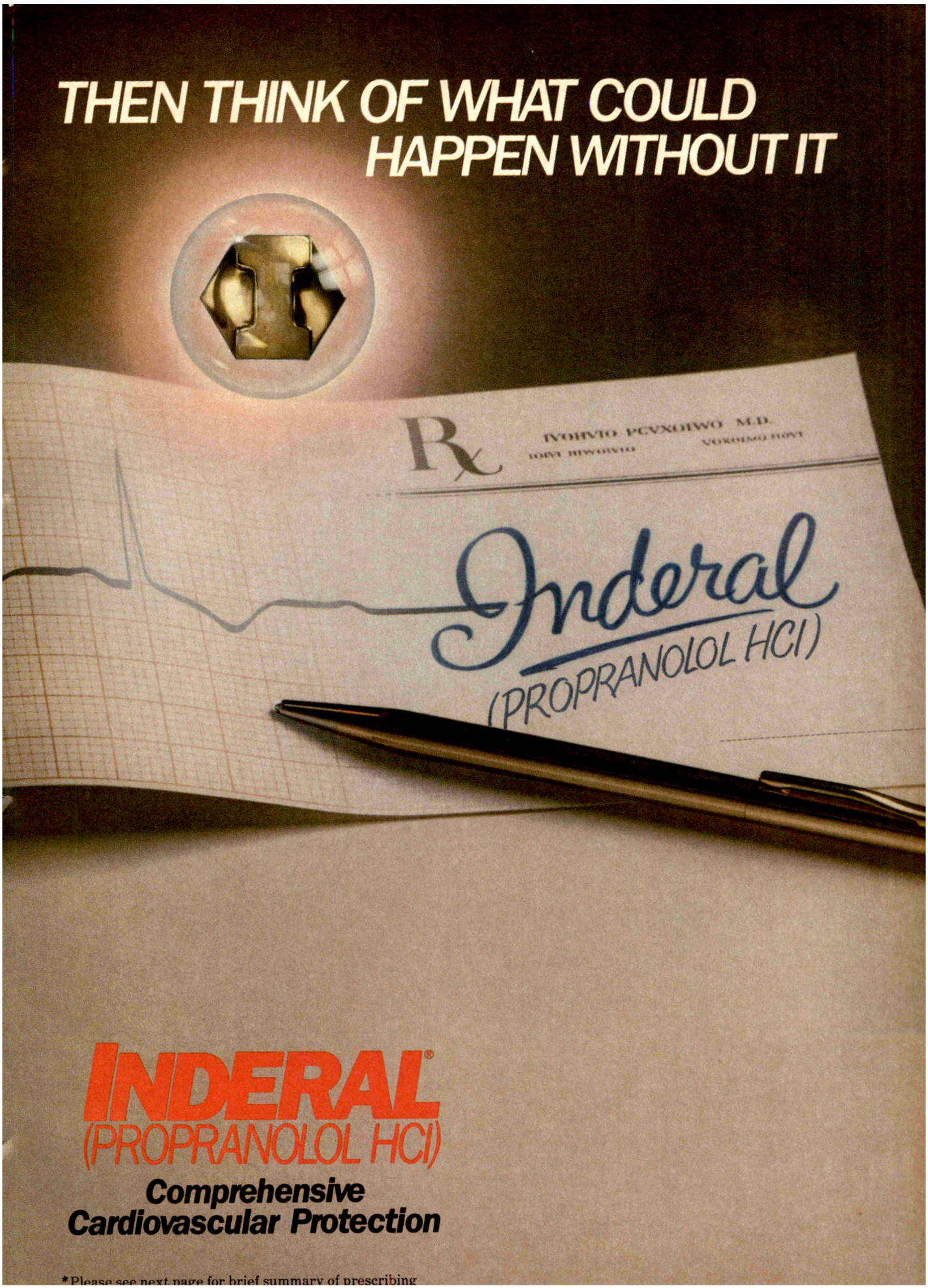
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® (propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

Propranolol hydrochloride is contraindicated in 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine-blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura. *Central Nervous System:* lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. *Gastrointestinal:* nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis. *Allergic:* pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress. *Respiratory:* bronchospasm. *Hematologic:* agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. *Miscellaneous:* reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol. *Clinical Laboratory Test Findings:* Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

HOW SUPPLIED

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Hemodynamic Effects of Felodipine at Rest and During Exercise in Exertional Angina Pectoris

JEAN-MARIE R. DETRY, MD, PATRICK M. De COSTER, MD, and JEAN RENKIN, MD

To examine the antianginal effects of felodipine, a new calcium antagonist, 8 patients with coronary artery disease and exertional angina pectoris were studied. Hemodynamic measurements were made at rest, during submaximal exercise and during angina-limited exercise before and 30 minutes after oral administration of 0.1 mg/kg of felodipine. Angina pectoris was always prevented after the drug was given and the exercise intensity was increased until recurrence of angina (5 patients) or exhaustion (3 patients). Hemodynamic data were also recorded at this higher exercise capacity. At rest and during submaximal exercise, felodipine increased heart rate and decreased arterial blood pressure and systemic vascular resistance. The prevention of angina pectoris was accompanied by lower mean pulmonary capillary wedge pressure, systemic vascular resistance and ST-segment depression; the pressure-rate product was unchanged. The 20% greater exercise capacity after felodipine was attended by a 20% increase in maximal cardiac output, a 17% increase in maximal heart rate and a 13% increase in maximal pressure-rate product; the maximal arterial blood pressure and ST-segment abnormalities were unchanged and the systemic vascular resistance was lower. The relation between ST-segment depression and the pressure-rate product during exercise was favorably influenced by felodipine.

Thus, felodipine is an active antianginal drug; its major mechanism of action is to lower the systemic vascular resistance. The data also suggest that it improves coronary blood flow during exercise.

(Am J Cardiol 1983;52:453–457)

Felodipine (4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid ethyl methyl-ester) is a newly developed calcium antagonist that, like nifedipine, is a dihydropyridine. Pharmacologic studies indicate that felodipine acts selectively on vascular smooth muscle, but its effects on the myocardium are less marked than those of nifedipine.[1–3] Previous clinical studies have shown that felodipine is a potent and well tolerated antihypertensive agent,[4,5] but little is known about its antianginal effects. The present study examines the antianginal effects of felodipine in a group of patients with exertional angina pectoris. Hemodynamic data were collected at rest and during submaximal and maximal exercise before and after 0.1 mg/kg of felodipine given orally.

Methods

Patients: Eight patients (6 men and 2 women, mean age 58 years) who had disabling and exertional angina pectoris were studied. The presence of significant coronary lesions was documented in all cases (Table I). Patients with a history of heart failure or systemic hypertension were excluded from the study; beta blockers and calcium antogonists were discontinued at least 48 hours before the start of the study. No serious complications occurred as a result of the experimental protocol.

Protocol: The patients first performed a multistage bicycle exercise test in the sitting position; the initial work load of 20 W for 1 minute was increased by 20 W each minute. Exercise was continued until the onset of typical angina pectoris. Electrocardiographic leads V_4, V_5 and V_6 were monitored on an oscilloscope and recorded on paper every minute during exercise and during the first 5 minutes of recovery. The electrocardiographic tracings were analyzed visually. The amount of horizontal ST-segment depression was measured 0.08 second after the J point, with the PR interval used as 0 reference. The main objective of this multistage exercise test was to determine the level of exercise that induced angina pectoris. This information served to determine the intensity of the exercise levels to be used during the hemodynamic study.

The next day, hemodynamic variables were measured with patients in supine and sitting positions at rest and during 2 levels of sitting exercise; each level lasted 5 minutes (Fig. 1). The intensity of the first level was well below the threshold for angina. The intensity of the highest exercise level was selected from the results of the first exercise test so that angina was induced after 3 to 4 minutes. Thus, hemodynamic data were obtained at rest, during submaximal exercise and during

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TABLE I Clinical Data in 8 Patients

Case	Age (yr)	Prior MI	Coronary arteriography*				Left ventriculography			
			LM	LAD	LC	RCA	Ant Wall	Apical Wall	Inf Wall	EF (%)
1	59	Inf	—	100	90	75	—	—	—	62
2	67	Inf	—	90	90	100	—	—	A	66
3	59	—	—	100	90	90	H	H	—	67
4	53	Ant	—	90	90	100	A	A	—	50
5	58	Inf	—	50	75	90	H	H	H	46
6	61	Ant	90	100	90	90	H	H	—	51
7	64	Inf	—	75	100	100	—	—	—	64
8	49	Inf	—	90	75	100	—	H	H	52

* Percent stenosis.

Abbreviations: A = akinesia; Ant = anterior; D = dyskinesia; EF = ejection fraction; H = hypokinesia; Inf = inferior; LAD = left anterior descending artery; LC = left circumflex artery; LM = left main coronary artery; MI = myocardial infarction; RCA = right coronary artery.

exercise-induced angina. After these measurements were completed, the patients rested in a supine position for 1 hour. After 30 minutes of rest, the patients were given felodipine orally (0.1 mg/kg of body weight).

Thirty minutes after felodipine was administered, the protocol was repeated. The hemodynamic variables were measured when the patients reached, without developing angina, the work level that had precipitated angina before felodipine treatment. The work load was then increased by 10 W/min until angina pectoris or the first signs of exhaustion appeared. That level of exercise was maintained for 5 minutes until hemodynamic measurements were completed (Fig. 1).

Hemodynamic measurements: Cardiac output was measured as previously described[6] at rest and during the last minute of each exercise period using the Fick principle. Briefly, a No. 7 Swan-Ganz balloon-tip catheter was percutaneously induced in the basilic vein and floated in the pulmonary artery; a small Teflon® catheter was introduced in the brachial artery. The pressures were measured during the 20 seconds preceding the cardiac output measurements with Statham P23Db transducers.

Precautions were taken to control factors that might influence the response to exercise.[6] The experiments were performed in the air-conditioned room with a temperature of 22 ± 1°C and relative humidity of 50 ± 10%.

Hemodynamic variables were calculated as follows: pressure-rate product = heart rate × systolic brachial pressure × 10^{-2}; systemic and pulmonary resistances = mean pressure × 80/cardiac output; and stroke work = stroke volume × mean brachial pressure × 1.36 × 10^{-2}.

The significance of differences was analyzed with a Student paired t test and McNemar test.

Results

Exercise capacity: The individual data on maximal exercise capacity are presented in Table II. Before felodipine administration, all patients were limited by exertional angina pectoris at a low exercise level (66 W). After felodipine, the symptom-limited maximal oxygen consumption increased from 1093 to 1314 ml/min (20%; $p < 0.001$), the maximal heart rate increased from 113 to 132 beats/min ($p < 0.001$) and the maximal systolic blood pressure was about the same, 157 versus 152 mm Hg (difference not significant [NS]). The pressure-rate product at maximal exercise increased significantly after felodipine, from 177 to 200 mm Hg/min^{-2} ($p < 0.02$), while the electrocardiographic abnormalities slightly but insigificantly decreased. All patients performed more work after felodipine and 3 were no longer limited by angina pectoris.

Hemodynamics at rest: At rest, the body position (supine or upright) did not influence the direction of the hemodynamic changes after felodipine, although these changes tended to be more marked and of greater statistical significance in the upright position. After felodipine, in the upright position, the cardiac output increased from 5.9 to 6.6 liters/min ($p < 0.001$) and the heart rate from 71 to 79 beats/min ($p < 0.001$). The systolic arterial blood pressure decreased from 138 to 126 mm Hg ($p < 0.001$) and, consequently, systemic vascular resistance was markedly reduced from 1480 to 1125 dynes s cm^{-5} ($p < 0.001$). The pressure-rate product and the mean capillary wedge pressure did not change.

Hemodynamics at submaximal exercise: The changes after felodipine during submaximal exercise were similar to those at rest. The heart rate increased from 96 to 109 beats/min ($p < 0.005$) and cardiac output from 8.4 to 9.2 liters/min (NS); the systolic arterial blood pressure decreased from 142 to 132 mm Hg ($p < 0.005$) and systemic vascular resistance from 987 to 851 dynes s cm^{-5} ($p < 0.02$). The pressure-rate product and the mean capillary wedge pressure did not change.

Changes in hemodynamics at maximal exercise: The work load that caused angina pectoris during the control study was always performed without pain after felodipine was administered. The prevention of angina pectoris was accompanied by a significant decrease in

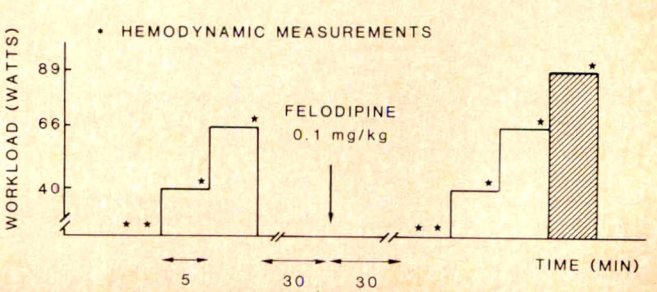

FIGURE 1. Protocol of the hemodynamic study.

TABLE II Data Collected at the Maximal Exercise Level Before and After Felodipine

Case		Work Load (W/min)	$\dot{V}O_{2SL}$ or $\dot{V}O_{2\ max}$ (ml/min)	Heart Rate (beats/min)	Systolic Blood Pressure (mm Hg)	Pressure-Rate Product (mm Hg/min^{-2})	Angina Pectoris	ST Depression (mm)
1	B	90	1397	103	190	196	Yes	0.6
	A	120	1772	139	180	250	No	0.3
2	B	60	1198	120	164	197	Yes	1.8
	A	90	1403	128	144	184	Yes	1.6
3	B	60	1032	108	150	162	Yes	3.1
	A	80	1236	128	135	173	Yes	1.9
4	B	100	1380	132	112	148	Yes	1.8
	A	120	1469	144	112	161	No	1.5
5	B	30	666	122	130	159	Yes	4.0
	A	40	813	138	126	174	Yes	3.9
6	B	40	707	105	184	193	Yes	0.9
	A	60	1001	132	176	232	Yes	0.7
7	B	30	738	91	164	149	Yes	1.1
	A	60	903	110	179	197	Yes	1.3
8	B	120	1627	125	164	205	Yes	3.2
	A	140	1918	139	160	222	No	3.3
Mean	B	66	1093	113	157	177	8/8	2.1
	A	89	1314	132	152	200	5/8	1.8
% change		−34	+20	+17	−3	+13		−14
	p	<0.001	<0.001	<0.001	NS	<0.02	NS*	NS

* McNemar test.
A = after treatment with felodipine; B = before treatment with felodipine; NS = difference not significant; $\dot{V}O_{2SL}$ and $\dot{V}O_{2Max}$ = symptom-limited and maximal oxygen consumption.

the mean capillary wedge pressure (from 24 to 19 mm Hg; $p < 0.05$) (Fig. 2). The heart rate increased from 113 to 119 beats/min ($p < 0.10$) and the systolic arterial pressure decreased from 157 to 146 mm Hg ($p < 0.02$); because these changes were in opposite direction, the pressure-rate product did not change. The electrocardiographic signs of myocardial ischemia were significantly reduced (ST depression from 2.1 to 1.3 mm; $p < 0.005$).

At the higher exercise level (Fig. 2, Table II), the increased oxygen consumption after felodipine was a result of the greater maximal cardiac output (from 9.3 to 11.2 liters/min [20%], $p < 0.05$), which was explained by a higher maximal heart rate, the maximal stroke volume was not modified. The maximal systolic blood pressure insignificantly decreased after felodipine and the maximal pressure-rate product increased. The ST-segment depression at maximal exercise insignificantly decreased after felodipine, from 2.1 to 1.8 mm.

Electrocardiographic changes during exercise: The relation between the ST-segment depression and pressure-rate product (Fig. 3) was altered by felodipine. After drug administration, there was a significantly smaller ST-segment depression for a similar pressure-rate product or the ST-segment depression was unchanged despite higher values of the pressure-rate product.

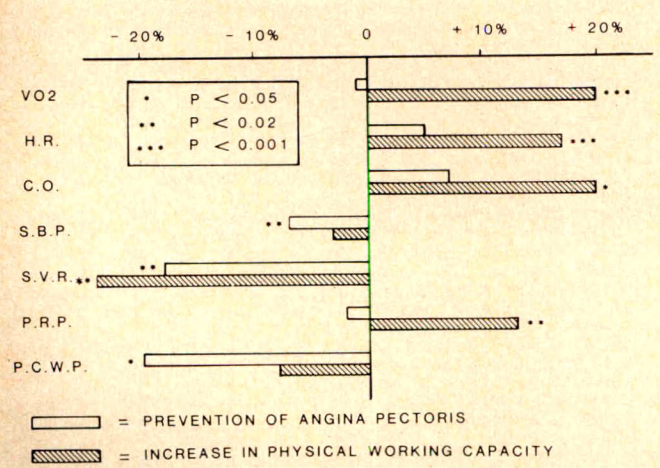

FIGURE 2. Hemodynamic changes at the maximal exercise level after felodipine. CO = cardiac output; HR = heart rate; PCWP = pulmonary capillary wedge pressure; PRP = pressure-rate product; SBP = systolic blood pressure; SVR = systemic vascular resistance; VO2 = oxygen consumption.

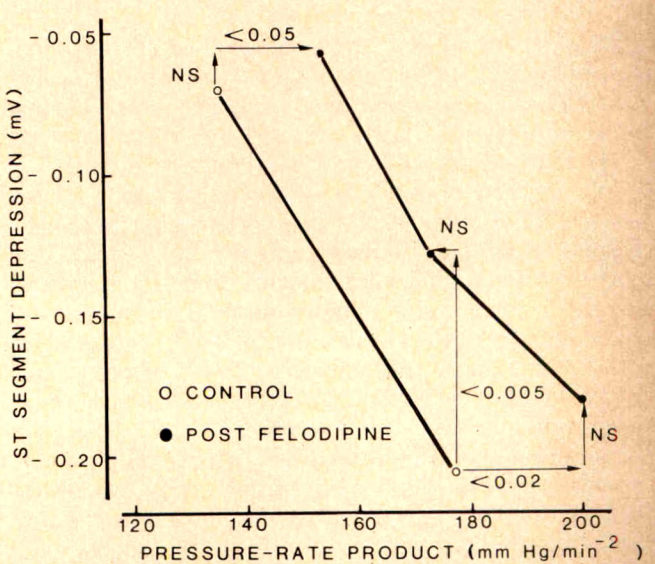

FIGURE 3. Effects of felodipine on relationship of pressure-rate product to ST changes during exercise.

Discussion

Our data indicate that felodipine has a significant antianginal effect. The exercise level that induced angina pectoris in all patients during the control study was always reached without pain 1 hour after felodipine was administered. Furthermore, after felodipine, all patients exercised at a higher level and 3 patients were no longer limited by angina. Felodipine induced a 20% increase in physical working capacity; this improvement is similar to that usually observed after other calcium antagonists[7–12] or after nitrates.[6,13] The major hemodynamic modification underlying this antianginal effect appears to be a decrease in systemic vascular resistance.

The protocol of the hemodynamic study included a first period of light exercise followed by a higher work load that induced angina pectoris in all patients within 4 to 5 minutes. When this protocol was repeated 60 minutes later, the reproducibility of the measurements was good for cardiac output, stroke volume, central pressures during exercise and pressure-rate product at the level of angina pectoris.[6,14,15] The hemodynamic modifications observed in our study can thus be safely attributed to the effect of felodipine and not to a placebo effect or to the simple repetition of the exercise test.

Hemodynamic effects during rest and exercise: The major effect of felodipine is to decrease the systemic vascular resistance. The lower blood pressure was attended by an increase in cardiac output and by a significant tachycardia. This increase in heart rate, suggesting a baroreceptor-mediated reflex, explains the lack of change in the pressure-rate product at rest and during exercise. Similar hemodynamic changes have been reported after nifedipine, a drug that increases heart rate and cardiac output and decreases systemic vascular resistance, while the pressure-rate product is usually unchanged.[16–18] These data differ from those collected after the administration of other calcium antagonists such as verapamil or diltiazem, which reduced the pressure-rate product at rest and during submaximal exercise.[7–10]

Prevention of angina pectoris: After receiving felodipine, all of our patients reached, without pain, exercise levels that had induced angina pectoris during the control period. At this exercise level, the exercise electrocardiogram was significantly improved and the filling pressure of the left ventricle was significantly reduced. These changes after felodipine indicate clearly that myocardial hypoxia was delayed, although the pressure-rate product was not significantly lower at that exercise level. Similar hemodynamic data have been reported for the effect of nifedipine.[19,20] At this level of exercise, the major mechanism of action of verapamil or ditiazem appeared to be a decrease in the rate-pressure product.[7–10]

Increased exercise tolerance: After felodipine, the exercise capacity of all of our patients was improved, and 3 of the patients were no longer limited by angina. This greater physical capacity was explained by the significantly higher maximal heart rate and maximal cardiac output. At the highest exercise level after felodipine, systolic blood pressure was similar to the control value and the maximal pressure-rate product was thus significantly greater than during the control period. This increase in the maximal pressure-rate product, while the ECG and hemodynamic abnormalities were not affected, suggests that the myocardial oxygen supply might have been improved by felodipine. This hypothesis is also supported by the change in the relation between the pressure-rate product and ST-segment depression.[21] Several investigators have reported that the improved exercise capacity of anginal patients after nifedipine was accompanied by an unchanged or increased maximal pressure-rate product together with a decrease in the ECG or scintigraphic signs of myocardial ischemia.[19,22–24] These results are best explained by an improved maximal coronary blood flow. Engel et al[25] showed that coronary flow to the ischemic zone was probably improved by nifedipine. After verapamil and diltiazem, the maximal pressure-rate product is probably unchanged, while the electrocardiographic abnormalities have been reported to be unchanged[7,10] or decreased[8,9] at the maximal exercise level. These findings have also been interpreted as suggesting that coronary blood flow is enhanced by calcium antagonists.

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Morphology of Ventricular Premature Beats as an Aid in the Electrocardiographic Diagnosis of Myocardial Infarction

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To determine whether morphologic analysis of ventricular premature beats (VPBs) can aid in the electrocardiographic diagnosis of myocardial infarction (MI), 12-lead electrocardiograms were evaluated in 760 consecutive patients who underwent cardiac catheterization, and 2-minute multiple-lead rhythm strips were evaluated in 515 of these patients. VPBs occurred in 58 patients; 21 had prior MI diagnosed by regional akinesia or dyskinesia on left ventricular cineangiography. Standard criteria were used to diagnose prior MI from the sinus beats of the electrocardiogram. Infarction was diagnosed from the morphology of a VPB when it had a QR or QRS pattern with Q wave ≥0.04 second.

Morphologic analysis of VPBs had a low sensitivity (29%) but high specificity (97%) and high predictive value (86%) for the diagnosis of MI. Sinus beats diagnosed MI with higher sensitivity (52%, and 69% if patients with left bundle branch block and left ventricular hypertrophy were excluded from analysis) than VPB morphologic analysis ($p < 0.05$), but with similar specificity (97%) and predictive value (92%). Two patients with angiographic MI had no MI according to standard electrocardiographic criteria, but did have an MI manifest by VPB morphologic analysis. Despite low sensitivity, analysis of the morphology of VPBs may be useful for the diagnosis of MI when the morphology of sinus beats is not diagnostic. Therefore, VPB analysis is complementary to the standard electrocardiographic diagnosis of MI.

(Am J Cardiol 1983;52:458-461)

In 1943, Dressler[1] reported that the morphology of ventricular premature beats (VPBs), by demonstrating pathologic Q waves, allowed him to make the electrocardiographic diagnosis of an acute myocardial infarction (MI) in a patient with left bundle branch block. Since his initial report, other anecdotal studies[2-6] have described the diagnosis of acute and healed MI from electrocardiographic morphologic analysis of VPBs. Although Bisteni et al[7] correlated the morphology of VPBs with experimental MI, the usefulness of this electrocardiographic sign has not been systematically studied in a population of patients at risk for cardiac disease. Moreover, there have been case reports of autopsy-proved false-positive diagnoses of MI from morphologic analysis of VPBs in patients with tuberculous pericarditis,[8] cor pulmonale[9] and valvular heart disease.[9] Consequently, we evaluated the relation between the morphologic characteristics of VPBs, baseline electrocardiographic findings, and the presence of MI identified at cardiac catheterization to document the value of VPB analysis in the diagnosis of old MI.

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Methods

Patients: We examined the electrocardiograms of 760 consecutive adult patients who had undergone diagnostic cardiac catheterization at the Milton S. Hershey Medical Center from December 1979 through February 1981. All patients had electrocardiograms the day before catheterization. The last 515 patients also had 2-minute, multiple-lead rhythm strips. Fifty-eight patients demonstrated VPBs and constitute the study population.

Cardiac catheterizations: All patients had coronary angiography performed by either the brachial or femoral approach. Significant obstructive coronary artery disease was defined as a stenosis of >70% luminal diameter. Of the 58 patients with VPBs, 33 had biplane left ventricular cineangiography and 25 had single-plane left ventricular cineangiography in the 30° right anterior oblique projection. Angiograms were evaluated by an investigator who had no knowledge of the clinical diagnosis or electrocardiographic findings. Left ventricular regional wall motion was evaluated qualitatively, and an angiographic diagnosis of MI was defined as a localized region of asynergy that showed akinesia or dyskinesia.[10,11]

Electrocardiographic analysis: Electrocardiograms were analyzed without knowledge of the clinical history or angiographic findings. Standard criteria[12] for the electrocardiographic diagnosis of MI from sinus beats were used: Anterior infarcts included those with pathologic Q waves ≥0.04 second in leads V_1 to V_3 (anteroseptal) or V_2 to V_4 (anteroapical). Lateral infarcts included those with pathologic Q waves in leads I, aVL and V_5 to V_6. Inferior and posterior infarcts included those with a Q wave ≥0.04 second and ≥25% of QRS deflection in lead aVF (inferior), or slurred R wave ≥0.04 second with R/S >1 in lead V_1 (posterior). When pathologic Q waves were present in the setting of other conditions that could account for the QRS abnormalities, such as left bundle branch block and left or right ventricular hypertrophy, MI was not diagnosed.

VPBs were defined according to the criteria of Chung.[13] MI was diagnosed from VPB analysis according to previously established criteria[4,12]: whenever a VPB showed a qR or qRS configuration with q wave ≥0.04 second. Lead aVR was excluded from analysis.

Statistical analysis: For the evaluation of the morphologic characteristics of VPBs, true-positive studies included those that met VPB criteria for an MI and had an angiographic diagnosis of MI. True-negative studies were those in patients without MI by VPB analysis and angiography. False-positive studies were those with an MI by VPB but not on angiography. False-negative studies denoted cases with an angiographically documented MI but no MI by VPB analysis. Similar criteria were used to correlate the diagnosis of MI based on sinus beats of the electrocardiogram with the data obtained from cardiac catheterization. For VPBs and sinus beats, sensitivity, specificity and predictive values were defined as follows: *sensitivity* = true positives/(true positives + false negatives); *specificity* = true negatives/(true negatives + false positives); and *predictive value* = true positives/(true positives + false positives).

The ability to diagnose MI by VPB morphologic analysis compared with sinus beats was evaluated by chi-square analysis with Yates' correction.

Results

Clinical characteristics: Of the 760 patients initially evaluated, 461 had coronary artery disease, 145 valvular heart disease, 16 primary dilated cardiomyopathy and 20 congenital heart disease; 118 patients were normal. Of the 58 patients with VPBs on the electrocardiogram, 29 had coronary artery disease, 27 had other cardiac disease and 2 were normal (Table I).

MI was documented at cardiac catheterization in 21 of 29 patients (72%) with coronary artery disease. All 21 patients had a region of akinesia or dyskinesia on the left ventriculogram with a total or subtotal occlusion of the coronary artery supplying the abnormal area. All 21 patients had a history of prolonged chest pain at rest; 14 were hospitalized at the time of pain and MI was confirmed by an abnormal increase in cardiac enzymes. Four of the 7 patients without enzymatic confirmation of MI had documentation by myocardial scintigraphy or necropsy. Two patients had MI diagnosed by redistribution thallium scintigraphy, and the location of MI corresponded to the region of asynergy seen on angiography. Two patients died within 1 week of catheterization and had old MI confirmed at autopsy, with the locations correlating to the areas of angiographic abnormality. The diagnosis of old MI independent of the angiographic or electrocardiographic data could not be confirmed in 3 patients.

TABLE I Clinical Characteristics of Patient Population

Coronary heart disease	29
(prior myocardial infarction)	(21)
Valvular heart disease	23
Dilated cardiomyopathy	3
Congenital heart disease	1
Normal	2
Total	58

Electrocardiographic analysis: Comparative sensitivity, specificity and predictive values for the diagnosis of MI from sinus beats and VPBs are given in Table II. MI was diagnosed from sinus beats of the electrocardiogram in 11 of 21 patients (sensitivity 52%). If the 5 patients with electrocardiograms that masked the diagnosis of MI (left bundle branch block in 2, left ventricular hypertrophy in 3) are excluded, the sensitivity of the electrocardiographic diagnosis of MI from sinus beats increases to 69%. There was a false-positive electrocardiographic diagnosis of MI (specificity 97%) in a patient with congenital subaortic stenosis. The predictive value of the standard electrocardiographic criteria for the diagnosis of MI was 92%.

MI was diagnosed by morphologic analysis of VPBs in 6 of 21 patients (sensitivity 29%). Three patients did not have VPBs in an electrocardiographic lead corresponding to the angiographic location of their MI. If these 3 patients are excluded from analysis, the sensitivity of the VPB criteria for the diagnosis of MI increases only to 33%. One patient without angiographic evidence of MI had VPBs with a morphology indicative of infarction (specificity 97%). He had severe aortic

TABLE II Value of Electrocardiography and Ventricular Premature Beat Morphologic Analysis in the Diagnosis of Myocardial Infarction

	ECG	ECG*	VPB	VPB*
Sensitivity	11/21 (52%)	11/16 (69%)*	6/21 (29%)	6/18 (33%)*
Specificity	36/37 (97%)	—	36/37 (97%)	—
Predictive value	11/12 (92%)	—	6/7 (86%)	—

* $p < 0.05$ ECG* versus VPB.*

ECG = sinus beats of electrocardiogram; ECG* = sinus beats excluding those in electrocardiograms with left bundle branch block or left or right ventricular hypertrophy; VPB = ventricular premature beats; VPB* = VPBs excluding those in electrocardiograms in which premature beats did not occur in leads likely to reflect myocardial infarction. See text for explanation.

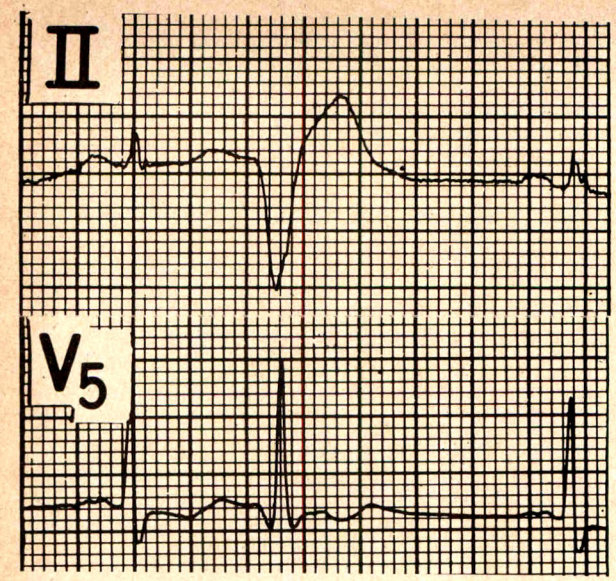

FIGURE 1. Simultaneous rhythm strip of leads II and V_5 from a patient with extensive inferolateral myocardial infarction at angiography. The 12-lead electrocardiogram was nondiagnostic for infarction, showing only a narrow Q wave in lead III. A ventricular premature beat in lead V_5 shows a QRS pattern with a pathologic Q wave.

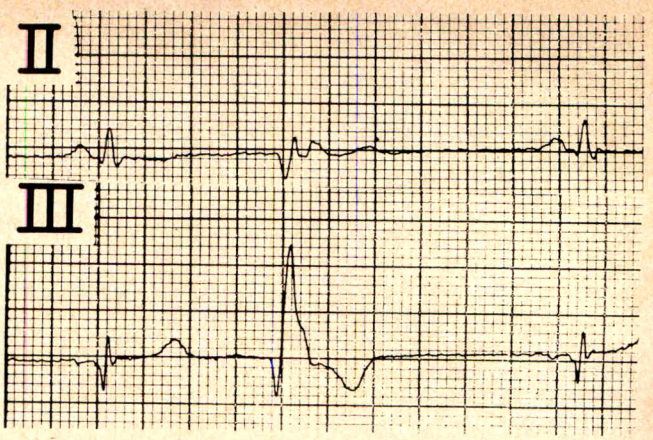

FIGURE 2. Simultaneous rhythm strip of leads II and III from a patient with a prior inferior myocardial infarction. The 12-lead electrocardiogram was nondiagnostic for infarction, with narrow Q waves in leads II, III and aVF and Q <25% of the total QRS deflection in lead aVF. The ventricular premature beat in leads II and III shows a QR pattern with a pathologic Q wave.

regurgitation, biventricular failure, and right atrial enlargement. The predictive value for the diagnosis of MI from the morphology of VPB was 86%.

There were no significant differences in the sensitivity, specificity or predictive value when comparing the two techniques in the diagnosis of MI. When the patients with left bundle branch block, left ventricular hypertrophy and no VPBs in the electrocardiographic leads corresponding to anatomic MI site are excluded from analysis, MI was diagnosed from sinus beats on the electrocardiogram with greater sensitivity ($p < 0.05$) than from VPB morphologic analysis.

Two patients with a documented MI did not have an MI on the sinus beats of the electrocardiogram, but had one according to VPB criteria. One had a large inferolateral MI at angiography with a totally occluded right coronary artery. A VPB in lead V_5 (Fig. 1) showed a pathologic QR pattern. The other patient had an inferior MI. VPBs in leads II and III had pathologic QR patterns (Fig. 2).

Discussion

Case reports,[1–3] while identifying the phenomenon of VPB morphologic characteristics suggestive of MI, do not determine the usefulness of the finding. Our results confirm that an analysis of the morphology of VPBs is highly specific for the diagnosis of MI and thus provides a complementary tool to the standard electrocardiographic diagnosis of MI. Such high specificity, however, depends on the use of strict criteria for making the diagnosis of MI from VPB morphology. Bisteni et al[7] showed in an experimental dog model that VPBs with QR or QRS pattern occurred only after MI, but that beats with a QS pattern could be produced in normal hearts.

Freundlich and Kavanagh-Gray[5] reviewed 20 electrocardiograms with VPBs that had a qR morphology suggestive of MI. Their patients had a history of angina or MI; 17 had an MI pattern on the sinus beats of the electrocardiogram, and the 3 others had an MI documented at autopsy. Although their study seems to confirm our findings of the high specificity of VPB morphologic analysis in the diagnosis of MI, they did not report the overall patient population from which they obtained their electrocardiograms. Anttonen et al[9] examined VPBs with qR patterns in the precordial electrocardiographic leads and found false-positive diagnoses of MI in 14 of 126 patients (specificity 89%). Twelve of these 14 patients had cor pulmonale or valvular heart disease and clinical evidence of right ventricular dilatation and right heart failure. Of interest, therefore, is a recent report[14] documenting marked right atrial enlargement as a cause of a qR pattern in the right precordial electrocardiographic leads. Our one patient with a false-positive diagnosis of MI by VPB morphologic analysis had severe aortic regurgitation with biventricular failure and right atrial enlargement documented at surgery.

Several limitations of our study should be mentioned. Despite the large number of patients accrued into the study, including 461 patients with coronary artery disease and many with prior MI, only 58 patients had VPBs. To identify more patients with prior MI and VPBs, it would be necessary to obtain multiple-lead rhythm strips over prolonged periods. Such a procedure would be cumbersome, impractical and costly.

Another potential limitation of our study was our method of identifying MI. Although akinetic and dyskinetic segments of myocardium usually correspond to transmural scar,[11] other investigators have demonstrated occasional improvement in regional contraction in such segments after administration of nitroglycerin[15] or after revascularization.[16] In our study all 21 patients with an MI defined angiographically had histories of

prolonged chest pain, and 18 had their MI confirmed independently by clinical history. Thus, it is unlikely that we had any false-positive diagnoses of MI.

Did we miss any MIs because 25 of the 58 patients did not have biplane left ventricular cineangiograms? No patient without an angiographic MI had a clinical history suggestive of MI. The only false-positive electrocardiogram was in a patient with congenital subaortic stenosis. The only false-positive MI by VPB morphologic analysis was in a patient with valvular heart disease. Both of these patients had biplane cineangiograms. It is doubtful, therefore, that we underdiagnosed MI in our patient population. In contrast, studies[6,9] of VPB morphology in the diagnosis of MI that relied on clinical history and laboratory data to diagnose MI probably underestimated the true incidence of MIs in their patient populations, because as many as 23% of MIs are unrecognized clinically.[17]

In conclusion, VPBs with morphologic characteristics indicative of MI occur infrequently; however, when they are seen, their high specificity and predictive value make them useful for the diagnosis of MI. The one major exception is the group of patients with right ventricular failure and right atrial enlargement in whom VPBs in the right precordial electrocardiographic leads may falsely suggest MI. Morphologic analysis of VPBs may be especially valuable when the resting electrocardiogram is nondiagnostic for MI, as in left bundle branch block, or, as is often the case, with an old inferior MI.

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Prognosis After an Initial Non–Q-Wave Myocardial Infarction Related to Coronary Arterial Anatomy

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Eighty-six consecutive hospital survivors (aged ≤60 years) of a first non–Q-wave acute myocardial infarction (MI) were followed up prospectively. Coronary arteriography was performed a median of 2 weeks after MI. The size of the MI was small (as judged by a mean peak creatine kinase level of 906 IU/liter); 90% were in Killip class I, and the mean left ventricular ejection fraction was 60 ± 11% (± standard deviation). Forty-nine patients had 1 vessel significantly narrowed by disease (≥70% luminal diameter reduction), 19 had 2-vessel, 2 had 3-vessel, 3 had left main (≥50% luminal diameter reduction), and 13 minimal or no coronary artery disease (CAD). Complete occlusion of the MI-related vessel was present in 33 patients. All 33 and an additional 5 patients had collateral vessels to the MI area. During a mean follow-up of 25 months, 1 cardiac death and 4 recurrent infarcts (3 with non–Q-wave MI) occurred. Angina occurred in 53 patients (62%) and responded medically in all but 7 who underwent coronary artery surgery. Angina after MI occurred frequently in patients with severe proximal left anterior descending CAD (≥90%), and in those with CAD (≥50%) in a vessel supplying collaterals to the infarct area.

Because angina can be managed medically in most patients and the outcome is good, routine coronary angiography is not indicated in asymptomatic survivors ≤60 years of a first non–Q-wave MI. (Am J Cardiol 1983;52:462–465)

Non–Q-wave acute myocardial infarction (MI) characterized by electrocardiographic ST-T-wave changes without the development of pathologic Q waves is a common clinical syndrome in patients admitted to a coronary care unit. Such infarcts are not necessarily transmural or subendocardial.[1,2] The late mortality rate after non–Q-wave MI has been reported to be comparable with Q-wave MI,[3,4] and some studies have demonstrated a high incidence of early[5] and late[6,7] recurrent MI after an initial non–Q-wave MI. Because of this reported high incidence, patients who sustain a non–Q-wave MI have been recommended for early coronary angiography and, when appropriate, coronary artery bypass surgery.[8]

Despite recent reports of the outcome of patients with non–Q-wave acute MI, little information is available about their coronary artery disease (CAD) and its relation to prognosis. In this prospective study, hospital survivors ≤60 years of age with a first non–Q-wave acute MI underwent early coronary angiography, and subsequent clinical events were correlated with the extent and severity of coronary artery obstruction.

Methods

Patients: Between November 1976 and February 1982, 380 consecutive patients ≤60 years of age with no other life-threatening diseases were discharged from our coronary care unit after an acute MI. Of these, 121 had electrocardiographic evidence of non–Q-wave MI. Thirty-three patients with non–Q-wave MI were excluded from this study because of 1 or more of the following criteria: previous MI (n = 14), in-

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TABLE I Coronary Angiographic Data

Number of Significantly Stenosed Vessels*	
Left main	3
3 vessels	2
2 vessels	19
1 vessel	49
0 vessel	13
Diameter reduction of IRV	
Occluded	33
>90 ≤99%	27
≥70 ≤90%	8
<70%	18
Collateral vessels present to IRV	38
Jeopardized collateral vessels† to IRV	17
Proximal LAD stenosis‡	20

* Luminal diameter reduction of ≥50% of left main or ≥70% of left anterior descending, circumflex or right coronary arteries.
† Arising from a vessel which is itself ≥50% stenosed.
‡ Left anterior descending arterial diameter reduction by ≥90% before the first septal or diagonal branch, or both.
IRV = infarct-related vessel; LAD = left anterior descending artery.

terhospital transfers (n = 17), cardiomyopathy (n = 3), and valvular heart disease (n = 1). Patients in whom infarct extension occurred in hospital were also excluded. Two eligible patients did not undergo angiography. Eighty-six survivors of a non–Q-wave MI form the study group. The age range was 27 to 60 years (mean ± standard deviation [SD] 49 ± 7).

Sixty-eight of the patients were men and 18 were women. Previous angina pectoris occurred in 52 (60%). Risk factors included 59 smokers, 28 with previously documented systemic hypertension, 9 with diabetes mellitus and 13 with a history of a parent or sibling who died of CAD at <55 years of age.

Non–Q-wave MI was diagnosed by a characteristic history of prolonged chest pain, an increase in serum creatine kinase levels to at least twice the normal level (MB isoenzymes were not routinely assayed) and the development of ST- or T-wave changes that persisted for at least 24 hours in the absence of pathologic Q waves. Q waves were considered pathologic if they were ≥0.03 second in duration and were one third or more of the R-wave amplitude.

Cardiac catheterization: Cardiac catheterization was undertaken a median of 2 weeks after MI (mean 3.8 ± 4.6, range 1 to 19). Ejection fraction was calculated from the 30° right anterior oblique left ventricular (LV) cineangiogram.[9] Significant coronary stenosis was considered present if there was ≥70% luminal diameter reduction of a major artery in any view or if there was ≥50% luminal diameter reduction of the left main coronary artery. All angiographic studies were reviewed by 3 experienced observers and reports were made by consensus.

Follow-up study: After hospital discharge, patients were attended by their own physicians and no attempt was made to influence their management. The mean duration of follow-up was 25 ± 18 months and was 100% complete.

Statistical evaluation of results and events was undertaken using the chi-square test. Pooled data are reported as mean ± 1 SD.

Results

The site of MI was anterior in 23 patients (27%), anterolateral in 31 (36%) and inferior in 32 (37%). Seventy-seven patients (90%) were in Killip class I, 6 were in class II and 3 were in class III. No patient developed cardiogenic shock. The mean peak creatine kinase measurement for the group was 906 ± 694, suggesting the infarct size was small. In the coronary care unit, 4 patients developed ventricular fibrillation or sustained ventricular tachycardia that required cardioversion.

Cardiac catheterization: The mean LV ejection fraction was 60 ± 11%. The details of CAD are shown in Table I. The infarct-related vessel was identified as the coronary artery supplying the area of abnormal contraction seen on the ventriculogram consistent with the electrocardiographically determined site of MI. In 33 patients this vessel was completely occluded. In these patients and in 5 with ≥90% stenosis of the infarct-related vessel, collateral vessels filled the infarct-related vessel beyond its proximal stenosis.

Clinical Outcome

Death: One patient died suddenly 14 months after an initial inferior infarct. At previous cardiac catheterization, 90% stenosis of the distal right coronary artery was present without other significant CAD. The ejection fraction was 58%. Stable angina pectoris occurred after hospital discharge and was controlled with beta-adrenergic blocking drugs. One noncardiac death occurred and was attributable to peritonitis.

Coronary artery bypass surgery: In 3 patients with left main disease and 1 patient with severe proximal left anterior descending (LAD) stenosis, surgery was undertaken within 1 month of cardiac catheterization. All 3 patients with left main CAD had severe angina in hospital after MI. In another 3 patients, surgery was undertaken later because of medically refractory angina. All 7 patients treated surgically are alive and free of angina a mean of 19 months after operation.

Recurrent myocardial infarction: Four patients had a late MI. In 3 it was a recurrent non–Q-wave MI in the area of the initial non–Q-wave MI. In the fourth patient, a Q-wave MI developed in the same area as the previous non–Q-wave MI. In 2 patients who experienced a recurrent MI in the same anatomic area as the original MI, early angiography demonstrated an occluded vessel supplying the infarct area.

Angina pectoris: Angina pectoris occurred after MI in 53 patients (62%). Neither hypertension nor cigarette smoking after MI were significantly related to angina after MI. However, 81% of patients who had angina before MI continued to experience angina after MI, whereas only 38% of patients without preinfarction angina experienced angina after MI ($p < 0.05$).

The extent and severity of CAD were related to angina after MI (Table II). Only 3 of 13 patients with insignificant coronary narrowing and 6 of 18 patients (33%) with <70% stenosis of the infarct-related vessel had post-MI angina. In contrast, 50 of 73 patients (68%) ($p < 0.05$) with significant (≥70% diameter reduction by disease) narrowing of ≥1 vessels and 47 of 68 patients (69%) ($p < 0.05$) with ≥70% stenosis of the infarct-related vessel had post-MI angina. The presence of severe proximal LAD disease (≥90% stenosis before the first septal perforator or first diagonal branch) and a jeopardized (≥50% stenosis) collateral blood supply to the infarct area appeared to be the most significant angio-

TABLE II Angiographic Data and Postinfarction Angina

Characteristic	n	Angina Present (%)	Angina Absent (%)	p Value
Multivessel disease*	24	19 (79)	5 (21)	<0.05
1-vessel disease	49	31 (63)	18 (37)	<0.05
0-vessel disease	13	3 (23)	10 (77)	<0.05
Infarct-related vessel				
100% occluded	33	26 (79)	7 (21)	<0.05
>90 ≤ 99% narrowed	27	16 (59)	11 (41)	<0.05
≥70 ≤ 90% narrowed	8	5 (62)	3 (38)	<0.05
<70% narrowed	18	6 (33)	12 (67)	<0.05
Proximal LAD disease†	20	18 (90)	2 (10)	<0.01
Collateral vessels present	38	31 (82)	7 (18)	<0.001
Jeoparized collateral vessels	17	17 (100)	0	<0.001

* Two or more vessels significantly stenosed.
† More than 90% stenosis of the left anterior descending coronary artery before the first septal or diagonal branch.

graphic predictors of post-MI angina. Eighteen of 20 patients (90%) with LAD stenosis and all 17 patients with jeopardized collateral blood supply developed post-MI angina.

Discussion

In these patients ≤60 years of age who survived a first non–Q-wave MI, only 1 cardiac death and 4 infarcts occurred during the 2-year mean follow-up period. They represent part of a larger series of patients with a good prognosis after MI.[10]

Angina pectoris after non–Q-wave MI occurred frequently but responded to medical therapy in most patients; 4 required surgery early and 3 later. All 3 patients with left main disease had medically refractory angina in the hospital after their initial MI and underwent early surgery. Angina was common in patients who experienced angina before MI. The most reliable angiographic predictors of angina after MI were severe proximal LAD disease or collateral vessels to the infarct area that arose from a stenotic artery.

Early exercise testing of the patients in this study was not routinely performed, but in our experience and in that of others it is a good predictor of patients who develop postinfarction angina.[11]

The outcome and extent of CAD in these patients is different from other reported series. This may be a result of different patient selection. All patients with previous MI or other significant cardiac or noncardiac disease and patients transferred from other hospitals because of complications were excluded from this study. Many studies of non–Q-wave MI have found a high rate of recurrent MI and cardiac death in the survivors, but have included patients with previous MI[3,4,6,7,12–15] and hospital-transferred patients.[4,6–8,13–16] The prognosis of patients who have had a previous MI is worse[17] and hospital transfer to a tertiary institution is usually for high-risk patients. Age is an important prognostic factor in CAD.[18] The mean age in our patients was 49 years, whereas in 2 previous studies the mean age was 66 and 63 years.[6,7] Other studies of younger patients with a first non–Q-wave MI revealed a prognosis similar to ours.[16,19]

Other studies have reported that the degree of LV impairment and the severity of CAD did not differ in patients with non–Q-wave and Q-wave MI, but again did not exclude those with previous MI.[8,14,20,21] A study comparable to ours showed that LV function is better and CAD less severe in patients with non–Q-wave MI.[22]

LV cineangiography in our patients demonstrated minimal impairment of LV function, suggesting that the size of the MI is small. Significant 1-vessel narrowing was found in 58% of patients and is partially explained by the younger age of the group and the fact that this MI was the first MI. The near-normal LV function and less severe CAD are the principal reasons that our patients have a good prognosis.

Clinical implications: Patients ≤60 years who survive a first non–Q-wave MI have a good prognosis. All 3 patients with significant left main CAD had severe MI after angina in the hospital and underwent operation. The patient who died and those who sustained late MI could not be retrospectively identified by knowledge of their CAD or LV function. Although angina pectoris after non–Q-wave MI was common, it was usually controlled satisfactorily by medical treatment. The degree and amount of CAD could not be predicted from the clinical data and was heterogeneous. Proximal LAD disease or jeopardized collateral vessels or both were usually associated with postinfarction angina.

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Effects Induced on Blood Platelets in Ischemic and Nonischemic Myocardium

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The function of blood platelets sampled from the coronary sinus and the superior vena cava was studied in 50 men with coronary artery disease at rest and during pacing-induced angina. At rest, a lower platelet aggregation and retention response was found in coronary sinus compared with vena caval blood. This may be due to refractoriness after previous platelet stimulation or to release of platelet inhibitors in the coronary circulation. During pacing-induced angina, lactate levels indicated that blood was sampled from ischemic myocardium in only 27 of the patients. Pacing-induced angina influenced platelet function differently in blood from ischemic and nonischemic regions. Adenosine diphosphate- and collagen-induced aggregation, platelet retention and plasma beta-thromboglobulin levels remained unchanged in blood from ischemic myocardium during pacing, but increased in blood from nonischemic regions. Thus, factors other than ischemia activated platelets in the coronary circulation during tachycardia-induced stress.

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Coronary artery thrombosis is not always found in acute myocardial infarction.[1] Coronary emboli, platelet microaggregates and arterial spasm have been suggested as causes of both transient and irreversible myocardial damage.[2,3] In a canine model,[4] the infusion of glass beads caused platelet microaggregation in the myocardial vessels and sudden death, which could be prevented by inhibition of platelet function.[4] Platelet aggregates have been found in epicardial arteries in patients who die suddenly,[5] suggesting that aggregates may have precipitated local ischemia and lethal arrhythmias. To examine the relation between coronary artery disease (CAD) and platelet function, blood has been sampled directly from the coronary sinus.[6–8] Differences in platelet function between parallel coronary sinus and aortic samples have been assumed to reflect changes induced in the coronary vessels, but the interpretation is difficult because general differences seem to exist in platelet function between arterial and venous blood.[9]

The present study compares platelet function in blood from the coronary sinus and the superior vena cava in patients with CAD to investigate effects of myocardial ischemia on platelet function. Atrial pacing was used to induce angina and lactate measurements to reveal myocardial ischemia.

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Materials and Methods

Heart catheterization was performed in 50 men as part of an evaluation for bypass surgery. All patients had typical angina and ST-segment depressions on the electrocardiogram (ECG) during an exercise test. None had taken aspirin for the last 10 days or beta blockers and calcium antagonists for the last 5 days. The 18 patients who smoked abstained from smoking for 12 hours before catheterization. Coronary angiography revealed CAD of more than 75% luminal diameter of at least 1 of the major coronary arteries in all but 2 patients, in whom 50% stenoses were found. Angiography was not performed in 1 patient.

After each patient gave informed consent, cardiac catheterization was performed with multipurpose catheters (polyurethane [Cordis®], 100 cm long, No. 8Fr). One catheter was advanced to the coronary sinus under fluoroscopic control and an identical catheter was positioned in the superior vena cava. A pacing electrode (Cordis®) introduced to the right atrium was connected with an external pacemaker (Cordis®) to allow an increase in heart rate by 10 beats every 2 minutes until angina developed. The ECG was monitored continuously from the precordial lead that gave the most pronounced ST-segment depression during the exercise test. The heart rate achieved during that test was an indicator of the extent to which the pacing rate had to be increased, but end points of pacing were angina and significant ST-segment depression. A venflon (Viggo®) was positioned in a femoral artery to allow sampling of arterial blood for lactate measurements. All catheters were kept open with continuous infusions of saline. No heparin was added. Blood was collected simultaneously from the coronary sinus and the vena cava for platelet function tests at rest and during maximal pacing. The lactate levels were measured in arterial and coronary sinus blood before, at the end of and 15 seconds after pacing.

TABLE I Platelet Function in Blood From the Superior Vena Cava and From the Coronary Sinus Sampled at Rest From 50 Patients with Coronary Artery Disease

	Superior Vena Cava	Coronary Sinus	
	Mean ± SD	Mean ± SD	p
Primary, ADP-induced aggregation (abritrary units)	14 ± 7	12 ± 7	<0.001
Collagen-induced aggregation (arbitrary units)	30 ± 13	27 ± 14	=0.07
Platelet retention			
Method A (%)	37 ± 14	26 ± 15	<0.001
Method B (%)	51 ± 17	43 ± 20	<0.005
Platelet counts (platelets/μl × 10^{-3})	235 ± 70	239 ± 64	NS
Circulating platelet aggregates (ratio)	0.91 ± 0.15	0.93 ± 0.13	NS
Plasma levels of Beta-thromboglobulin (ng/ml)	74 ± 30	77 ± 28	NS
Platelet counts in PRP (platelets/μl × 10^{-3})	380 ± 122	376 ± 117	NS

ADP = adenosine diphosphate; NS = not significant; p = level of significance; PRP = platelet-rich plasma; SD = standard deviation.

The following platelet functions were measured: Platelet aggregation was induced in an aggregometer (Payton) in platelet-rich plasma (PRP).[10] PRP was produced by centrifugation of blood collected into tubes containing 0.1 *M* sodium citrate. Adenosine diphosphate (ADP), 1.5 μmol/l, and collagen, 5 ng/ml in final concentrations (both Sigma Chemical Co.), were used as inducers. The aggregation response was read as the maximal rate of the primary, ADP-induced or collagen-induced aggregation and was calculated in arbitrary units as previously described.[11] No corrections were made for variations in platelet counts,[10] since they were similar in parallel PRP samples both at rest and during pacing.

Platelet retention was measured with Hellem's modified technique,[12] counting the platelets before and after native blood was forced at a constant rate through a glass bead column. Using *Method A*, 0.9 ml of blood was examined; using *Method B*, 3.6 ml was examined. Platelet counts were determined in triplicate in an automatic Coulter counter.

Beta thromboglobulin (βTG) was measured with a radioimmunoassay (Amersham). Blood was sampled into precooled vials containing ethylene diamine tetraacetate (EDTA), theophylline and prostaglandin E_1.[13] Plasma was separated after centrifugation for 30 minutes at 2000 *g* and, subsequently, for 30 minutes at 5000 *g* before freezing and analysis.

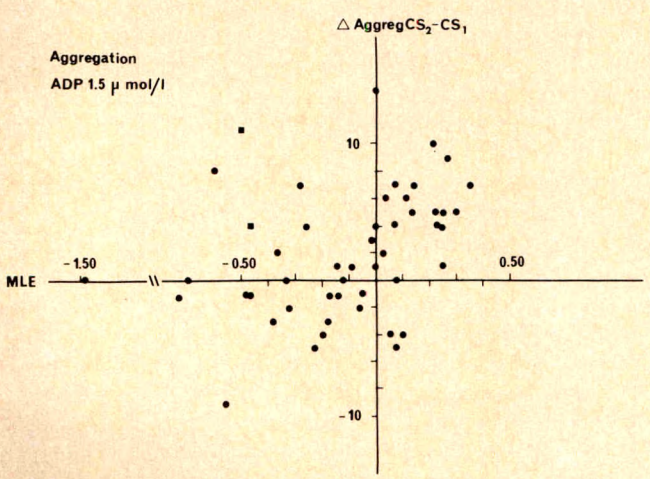

FIGURE 1. Relation between myocardial lactate extraction (MLE) during pacing and the difference between adenosine diphosphate–induced aggregation in coronary sinus blood at rest (CS_1) and during pacing (CS_2). Squares represent patients in whom the catheter was positioned rather distal in the coronary sinus.

The presence of circulating platelet aggregates in whole blood was estimated as described by Wu and Hoak.[14] A ratio of the platelet counts in PRP prepared with EDTA to platelet counts in PRP prepared with EDTA and formalin was determined. A ratio <1 reflects the presence of circulating platelet aggregates.

Lactate levels in plasma were measured to confirm whether ischemia was induced. Two milliliters of blood were added to precooled vials containing perchloric acid before centrifugation. The lactate levels were determined in triplicate.[15] Myocardial lactate extraction (MLE) was calculated as the difference between aortic and coronary sinus lactate levels divided by aortic lactate levels.

Statistics: The results are given as mean ± standard deviation. Differences between parallel or repeated measurements were determined with a Student *t* test. The coefficient of correlation was assessed with Hewlett Packard computerized programs and the coefficient of variation (CV) as described elsewhere.[16]

Results

All 50 patients had pacing-induced angina and 40 had ST-segment depression; net myocardial lactate production occurred in only 27. These 27 "ischemic" patients are considered separately because platelets were sampled from predominantly ischemic regions in them. In the ischemic patients the mean MLE at rest, during pacing and immediately after pacing was 0.19 ± 0.12, −0.13 ± 0.24 and −0.40 ± 0.33, respectively. In the 23 "nonischemic" patients, the corresponding values were 0.24 ± 0.10, 0.20 ± 0.05 and 0.15 ± 0.11. The heart rate during maximal pacing was 125.2 ± 13.7 beats/min in ischemic patients and 125.7 ± 15.0 beats/min in nonischemic patients.

At rest, the primary ADP-induced aggregation and the retention values were moderately but significantly lower in coronary sinus than in vena caval blood (Table I). The βTG plasma levels, platelet counts and circulating platelet aggregates were similar in the parallel venous samples.

Atrial pacing had no effect on platelet function in coronary sinus blood in the 27 ischemic patients (Table II). In the 23 nonischemic patients, however, platelets were activated, as judged from a 28% increase in ADP-induced aggregation, a 13% increase in collagen-induced aggregation, a 50% increase in platelet retention as measured with Method A, and a 26% increase in plasma

TABLE II Platelet Function in Coronary Sinus Blood at Rest and During Pacing-Induced Angina in 27 Patients in Whom Blood Was Collected From Ischemic Myocardium and 23 in Whom Blood Was Collected From Nonischemic Myocardium

	Ischemic Group			Nonischemic Group		
	Rest Mean ± SD	Angina Mean ± SD	p	Rest Mean ± SD	Angina Mean ± SD	p
Primary, ADP-induced aggregation (arbitrary units)	12 ± 7	12 ± 6	NS	12 ± 7	15 ± 9	<0.01
Collagen-induced aggregation (arbitrary units)	24 ± 14	24 ± 15	NS	31 ± 14	35 ± 15	NS
Platelet retention						
Method A (%)	30 ± 16	32 ± 15	NS	23 ± 13	34 ± 13	<0.005
Method B (%)	45 ± 20	48 ± 20	NS	41 ± 19	45 ± 18	NS
Platelet counts (platelets/μl × 10^{-3})	238 ± 81	232 ± 80	NS	239 ± 38	247 ± 54	NS
Circulating platelet aggregates (ratio)	0.87 ± 0.16	0.92 ± 0.12	NS	0.97 ± 0.15	0.78 ± 0.24	NS
Plasma levels of Beta-thromboglobulin (ng/ml)	76 ± 27	71 ± 23	NS	79 ± 29	99 ± 50	<0.05
Platelet counts in PRP (platelets/μl × 10^{-3})	373 + 144	363 ± 141	NS	380 ± 77	368 ± 108	NS

ADP = adenosine diphosphate; p = level of significance; PRP = platelet-rich plasma; SD = standard deviation. Methods A and B are described in the text.

βTG levels. In the 5 nonischemic patients in whom circulating platelet aggregates were measured, a decreased ratio reflected an increased amount of circulating aggregates. In patients with 1- or 2-vessel disease, ADP-induced aggregation increased in 18 of 22 patients, compared with 9 of 27 with 3-vessel disease ($p < 0.001$) (Fig. 1). Platelet aggregation increased in most patients with a positive MLE (Fig. 2), while in patients with a negative MLE, it decreased in some and increased in some.

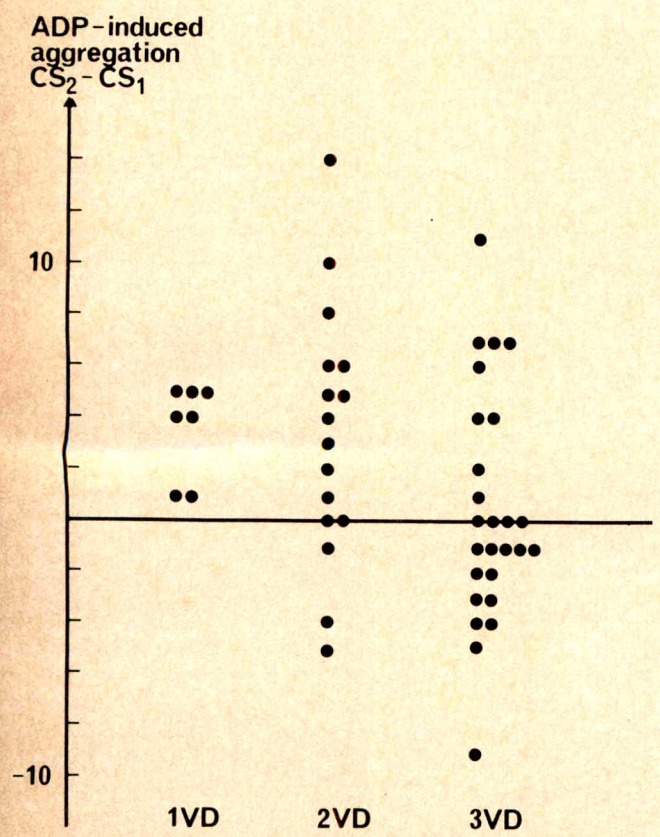

FIGURE 2. Relation between 1-, 2- or 3-vessel disease (1VD, 2VD, 3VD) and the difference between adenosine diphosphate–induced aggregation in coronary sinus blood at rest (CS_1) and during pacing (CS_2).

Platelet function was similar during 2 consecutive pacing episodes separated by a 45-minute interval. Thus, for ADP-induced aggregation, $r = 0.83$ ($p < 0.001$) and CV = 26.5, and for collagen-induced aggregation, $r = 0.86$ ($p < 0.001$) and CV = 29.7. The retention response showed greater variability: Method A, $r = 0.26$ ($p > 0.10$) and CV = 48.8; Method B, $r = 0.52$ ($p < 0.01$) and CV = 40.9. For plasma βTG levels, $r = 0.71$ ($p < 0.01$) and CV = 27.0. For total platelet counts in native blood, $r = 0.94$ ($p < 0.001$) and CV = 11.9, and for platelet counts in PRP, $r = 0.92$ ($p < 0.001$).

Discussion

The clinical recognition of myocardial ischemia may be difficult. Angina can occur without evidence of insufficient myocardial blood supply[17] and transient ST-segment changes may indicate ischemia in the absence of chest pain.[18] Lactate levels were measured in the present study not only to detect ischemia, but also to verify that the coronary sinus blood drained ischemic myocardium. The finding of net lactate production in only half of the patients with pacing-induced chest pain demonstrates that ST-segment changes or pain alone did not ensure that blood would be collected from ischemic myocardium. Pacing-induced myocardial ischemia as measured with lactate metabolism or ST-segment depressions has been reported to be highly reproducible.[19]

Platelet function was reduced in blood that had passed the arteriosclerotic coronary vessels at rest, in agreement with previous reports.[6,8,11] Possible mechanisms may be refractoriness after mild platelet stimulation or the effect of platelet inhibitors released in the coronary vessels.

Surprisingly, platelets were, on the average, unaffected in coronary sinus blood during pacing in the ischemic patients. In agreement with these results, others[20] reported that patients with an ischemic lactate response did not increase the coronary sinus plasma levels of platelet factor 4 during pacing. In another study,[7] platelet aggregation was reduced in coronary sinus blood during pacing in patients with net lactate production. The finding of enhanced aggregation during

pacing in another study[6] is difficult to interpret because ischemia was not biochemically verified.

Most patients with 3-vessel disease developed a net lactate production. In these patients, the mean platelet aggregation was unchanged during pacing, while, on the average, the aggregation increased in patients with 1- and 2-vessel disease owing to a high proportion of nonischemic patients in whom platelets were almost uniformly activated. This activation is in agreement with the results of a study in healthy subjects with a nonischemic lactate response to pacing.[7] In another study[6] in which lactate measurements were not included, in patients with chest pain but normal coronary angiograms, platelet aggregation was unchanged in coronary sinus blood during pacing.

The present results suggest that factors other than ischemia induce platelet activation in the coronary circulation. A lack of activation in ischemic zones may be salutary and may explain why anginal episodes do not progress into irreversible myocardial damage more often. The mechanism of activation in nonischemic regions is not apparent, but reports of more pronounced catecholamine release from nonischemic than ischemic myocardium during stress and a good correlation between platelet activation and catecholamine release fit with the present results.[21,22] However, platelets are modulated by a number of factors. The proaggregatory thromboxane A2 as well as antiaggregatory prostacyclin are both released during stress.[23] The net effect of these and other mediators of platelet function is difficult to predict, and emphasizes the advantage of studying measurements of platelet responsiveness itself.

The present study reveals that platelets are affected differently in ischemic and nonischemic myocardium, and since coronary sinus blood is a mixture of blood from these regions, the degree of platelet activation during pacing probably depends upon whether the dominating proportion of the coronary sinus blood is sampled from ischemic or from nonischemic zones. The changes induced during pacing were moderate, but could be detected, because the influence of the sampling procedure on the platelets is mild.[11]

Animal studies and autopsy findings suggesting that platelet aggregation may cause plugging of coronary vessels, resulting in myocardial necrosis,[4,5,24] have been supported by the demonstration of platelet activation in nonischemic myocardium during tachycardia stress. Thus, an improved prognosis in coronary artery disease may be achieved not only by antianginal regimens that reduce myocardial ischemia, but also by specific platelet inhibition, which may be beneficial to patients with arteriosclerotic heart disease.

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Clinical Data Versus Noninvasive Testing as an Estimate of Coronary Status

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The step from coronary angiography to surgery is taken primarily on the basis of the ejection fraction (EF) and number of diseased vessels (NV), taken jointly as coronary status (CS). This study reviewed (1) how well EF, NV and CS are estimated from clinical data, (2) how much improvement is gained by adding noninvasive data, (3) how good this model is when applied to a larger cohort and (4) whether the decision to angiography can be made on the basis of CS estimated from clinical data alone. A quantitative definition of CS was established as a principal component of EF and NV. Estimates of EF, NV and CS were made from clinical data of 60 patients. Correlations with the actual values were EF 87%, NV 93% and CS 93%. When noninvasive data were added to this model, the correlations increased to EF 95%, NV 99% and CS 98%. When the clinical data model was applied to 169 patients, the correlations decreased to EF 77%, NV 71% and CS 74%.

CS estimated from clinical data alone was set up as a test for angiography for 169 patients. This test had a sensitivity of 98% and a specificity of 63%, demonstrating the feasibility of using clinical data alone in deciding angiography.

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Angiography has emerged as the most definitive procedure for assessing coronary disease. It is a critical step on the path of clinical data, noninvasive testing, angiography and surgery. In this report, we discuss the decision to perform angiography. This decision, however, is overshadowed by the decision to perform surgery. Results of angiography can be summarized in terms of ejection fraction (EF) and number of diseased vessels (NV). These variables are jointly evaluated, usually subjectively, in terms of a single decision criterion, which we call coronary status (CS). To deal with these concepts quantitatively, we formalize a definition for CS (Fig. 1). A low CS indicates surgery, a high value no surgery, and an intermediate value requires that other factors be brought into consideration.

Investigators have set up EF and NV as standards for evaluating noninvasive tests. Several studies have related these test results, such as ST-segment depression, with coronary anatomy.[1–3] Further refinements have combined test results with clinical data to make angiographic predictions.[3–8] Using test results in addition to clinical data alone increases the costs and decreases the number of patients to whom these methods can be applied; for example, patients with unstable angina who cannot exercise.

For this study, we reviewed the charts of a limited number of patients who had angiography. The questions explored were (1) How well are EF, NV and CS estimated from clinical data? (2) How much improvement is gained by adding noninvasive data? (3) How good is this model when applied to a larger cohort? (4) Can the decision to perform angiography be made on the basis of CS estimated from clinical data alone?

Methods

Two groups of patients were studied. Group I included 60 patients who had clinical data and noninvasive tests. Group II included 109 patients who had clinical data alone. The Group I study evaluated clinical data and noninvasive tests as predictors of EF, NV and CS. The Group II study further defined the predictive ability of the clinical data derived from the Group I patients in a more heterogeneous patient group. The period of study was 1975 to 1978.

The patients underwent cardiac catheterization either to diagnose presence or quantitate the degree of disease. Each patient was suspected of having coronary artery disease or congestive heart failure unrelated to valvular disease. Patients were excluded if they had obvious valvular disease or a contraindication to any of the studies.

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Data: Every patient had a history and physical examination, electrocardiogram, and determination of EF, NV and CS. The Group I patients also had a chest roentgenogram, exercise stress test and ultrasound analysis. Table I defines the variables and how they were coded. Unspecified codes were absent 0, present 1.

Histories were obtained from chart review. Angina pectoris was diagnosed from retrosternal chest pain produced by effort and relieved by nitrates or rest. Hypertension was diagnosed from a history of receiving medication for hypertension or a resting blood pressure over 140/90 mm Hg. Diabetes was diagnosed if the patient so indicated when asked. Congestive heart failure was diagnosed if the patient complained of dyspnea or orthopnea or had dependent rales.

A standard 12-lead electrocardiogram was evaluated using New York Heart Association criteria.[9] One modification was the acceptance of ≥30 ms Q-wave duration in lead aVF as an indication of inferior infarction.

A standard posteroanterior view of the chest was evaluated. Blood redistribution to the upper lobes was estimated using the technique of Turner et al.[10] Heart size estimates from the chest film were derived from a table based on height and weight and expressed as a percentage of predicted normal.[11]

Each patient performed a standard treadmill stress test, using the Bruce protocol and 12 leads. The entire test was scanned for evaluation of ST-segment depression (start of exercise to 5-minute recovery). If ST-segment depression was present initially, a change in the depth of the ST segment was recorded. The ST segment was evaluated 80 ms after the J point. Blood pressure and heart rate were measured by sphygmomanometer and electrocardiogram, respectively.

M-mode echocardiograms were performed using a Unirod-D echocardiogram interfaced with a Honeywell fiberoptic recorder. A single view of the ventricle recorded in the standard transducer position was used for measurement. The measurements presented were determined using previously published guidelines.[12]

EF and NV were combined to provide a more global measure of the CS. This was done using BMDP4M factor analysis,[13] which, in essence, transforms the 2 measures into stan-

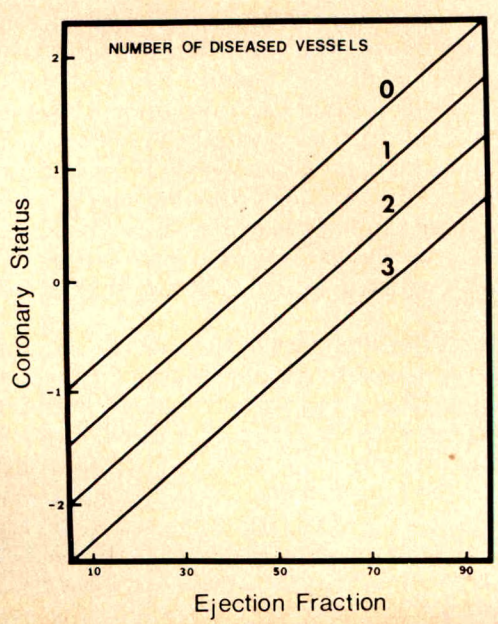

FIGURE 1. Coronary status as a function of ejection fraction and number of diseased vessels.

TABLE I Study Variables, Specification, and Coding (unspecified codes are no 0, yes 1)

I. History and physical
- 1 Age at diagnosis (years)
- 2 Sex (male 1 female 2)
- 3 Caucasian
- 4 Months since myocardial infarction (−12 if none)
- 5 Number of myocardial infarctions
- 6 Family history of heart attacks
- 7 Typical chest pain
- 8 Nontypical chest pain
- 9 Resting chest pain typical of coronary insufficiency
- 10 History of smoking
- 11 History of diabetes
- 12 Treatment with digitalis
- 13 Treatment with diuretic
- 14 Hypertension requiring treatment
- 15 Exertional dyspnea, orthopnea or paroxysmal dyspnea
- 16 History of edema
- 17 Height (in)
- 18 Ponderal index (lb/(height × height)
- 19 Systolic blood pressure
- 20 Diastolic blood pressure
- 21 Heart rate (beats/min)
- 22 Rales or wheezes
- 23 Apical systolic murmur
- 24 Harsh basilar systolic murmur
- 25 S_3
- 26 S_4
- 27 Pretibial edema
- 28 Distended neck veins

II. Electrocardiographic variables
- 29 Anterior infarction
- 30 Lateral infarction
- 31 Posterior infarction
- 32 Inferior infarction
- 33 Anterior ischemia
- 34 Lateral ischemia
- 35 Inferior ischemia
- 36 Left ventricular hypertrophy
- 37 Left atrial enlargement
- 38 Right atrial enlargement
- 39 Conduction defect
- 40 Premature atrial beat
- 41 Premature ventricular beat
- 42 Atrial fibrillation

III. Roentgenographic variables
- 43 Transverse cardiac diameter (percent normal: 90–110)
- 44 Left ventricular enlargement (none = 1,2,3,4 = marked)
- 45 Right ventricular enlargement (none = 1,2,3,4 = marked)
- 46 Other chamber enlargement (none = 1,2,3,4 = marked)
- 47 Pulmonary vascular congestion (none = 1,2,3,4 = marked)
- 48 Chronic obstructive airway disease

IV. Exercise stress test variables
- 49 Angina pain present
- 50 Maximal heart rate
- 51 Double product at maximal exercise: (0.01 × systolic blood pressure × heart rate)
- 52 Stage ST-segment depression of ≥1 mm
  1. 1.7 mph, 10% grade
  2. 2.5 mph, 12% grade
  3. 3.4 mph, 14% grade
  4. 4.2 mph, 16% grade
  5. No ST-segment change
- 53 Stage patient has chest pain or fatigue (as above)
- 54 Decrease in blood pressure of ≥10 mm Hg
- 55 ST-segment depression at maximal exercise (mm)

V. Echocardiographic measurements
- 56 Left ventricular internal dimension in diastole (normal 3.5–5.7)
- 57 Left ventricular internal dimension in systole
- 58 Fiber shortening (LVIDd-LVIDs)/LVIDd (normal 0.24–0.46)
- 59 EPSS (mm) from E point of mitral valve to septal surface
- 60 Posterior wall excursion (normal 0.9–1.4)
- 61 Septal excursion (normal 0.3–0.8)
- 62 Myocardial scar present
- 63 B notch in mitral valve

VI. Angiographic measures
- 64. Number of diseased vessels
- 65 Ejection fraction
- 66 Coronary status (combined number of diseased vessels and ejection fraction)

LVIDd = diastolic left ventricular internal diameter; LVIDs = systolic left ventricular internal diameter; EPSS = E point to septal surface.

TABLE II Variables Significantly Correlated with Number of Diseased Vessels or Ejection Fraction—Variable Means, Standard Deviations, and Correlations with Angiographic Variables

Study Variable	Mean Group I	Mean Group II	Mean Both Groups	SD	Angiographic Variable NV	EJ	CS
I. History and physical							
1 AGE	47.10	53.83*	51.44	10.41	0.33†	0.12	−0.14
2 MALE	1.34	1.22	1.26	0.44	−0.28†	0.14	0.29†
4 LASTMI	15.07	10.37	12.04	42.53	0.28†	−0.24‡	−0.36†
5 MINUMBER	0.59	0.52	0.55	0.70	0.39†	−0.30†	−0.47†
7 ANGIPAIN	0.47	0.57	0.54	0.50	0.33†	0.27†	−0.04
12 DIGITALS	0.23	0.29	0.27	0.43	−0.09	−0.35†	−0.18§
15 DYSPNEA	0.28	0.23	0.25	0.43	−0.23‡	−0.32†	−0.06
19 SYSTOLIC	121.27	129.61*	126.65	22.70	0.11	0.33†	0.15
25 S_3	0.17	0.11	0.13	0.33	−0.05	−0.39†	−0.23‡
28 NECKVEIN	0.04	0.08	0.06	0.24	−0.05	−0.27†	−0.15
II. Electrocardiographic variables							
29 ANTERINF	0.23	0.14	0.17	0.37	0.21‡	−0.34†	−0.37†
32 INFERINF	0.24	0.28	0.27	0.45	0.30†	−0.18§	−0.32†
37 LATRENLR	0.16	0.22	0.20	0.40	−0.13	−0.27†	−0.09
38 RATRENLR	0.03	0.05	0.05	0.21	−0.05	−0.32†	−0.18§
III. Roentgenographic variables		...	...	...	...	...	...
IV. Exercise stress test variables							
50 MXHTRATE	147.09	...	...	22.37	−0.45†	0.07	0.31§
V. Echocardiographic measurements							
56 LVIDDIAS	4.93	...	...	1.08	0.09	−0.50†	−0.38‡
57 LVIDSYST	3.51	...	...	1.08	0.16	−0.55†	−0.45†
59 EPSSINMM	7.67	...	...	6.09	0.18	−0.62†	−0.51†
62 MYOCSCAR	0.07	...	...	0.26	0.10	−0.43†	−0.34‡
VI. Angiographic measures							
64 NV	2.05	1.79	1.88	1.28	1.00†	−0.09	−0.74†
65 EJ	55.00	61.00*	59.00	0.18	−0.09	1.00†	0.74†
66 CS	−0.24	0.12*	−0.01	1.00	−0.74†	0.74†	1.00†

For complete listings of study variables, see Table I.
* Significantly different from Group I.
† $p < 0.001$.
‡ $p < 0.01$.
§ $p < 0.05$.

dard scores, which were averaged. The resulting CS value has a mean of 0.0 and a standard deviation of 1.0. Figure 1 shows how CS is derived from any combination of EF and NV. Positive values of CS are a consequence of a high EF and low NV. In general, a CS >0 translates into a no-surgery decision, a CS < −1 implies surgery, and −1 < CS < 0 is equivocal. As a basis for comparison, we adopt the convention that a CS > −0.5 is a decision for no surgery and a CS < −0.5 is a decision for surgery.

Analysis: Statistical analysis was done using biomedical computer program BMDP2R stepwise regression.[13] For each variable, the mean, standard deviation and correlations with the angiographic findings were calculated. For the Group I patients, variables were found that were significantly predictive when taken together. This was done in a sequential manner: (1) examining the history and physical and electrocardiographic variables, (2) augmenting these by the chest roentgenographic variables, (3) augmenting these by the exercise stress test variables and (4) further augmenting by the echocardiographic variables. Predictive ability was measured in terms of the standard error of estimate, which is the standard deviation of the predicted from the actual value. To explore the generality of the methods, all 169 patients were treated as a single group to develop predictive models based on the history and physical and electrocardiographic variables.

Results

Table II is a summary of the data from the 2 groups for variables significantly correlated with the angiographic findings. Group II was older, but had an average higher EF. The older patients had a higher NV. Males had fewer NV and better CS. The time since last myocardial infarction and the number of previous infarctions were adverse (i.e., had a worse CS). Angina was associated with a greater NV but higher EF. The use of digitalis was related to a lower EF. Exertional dyspnea appeared in conjunction with a lower EF but a lower NV. Exertional dyspnea appeared in conjunction with a lower EF but a lower NV. A higher systolic blood pressure was found with a higher EF. The presence of distended neck veins or an S_3 suggested a lower EF. Of the electrocardiographic variables, only inferior infarction was strongly indicative of NV and, thereby, a diminished CS. Anterior infarction and left or right atrial enlargement implied a lower EF. A higher exercise maximal heart rate was related to fewer NV. Four of the echocardiographic measurements had a high correlation with lower EF.

Table III is a summary of the ability of sets of noninvasive variables to predict the angiographic measurements. This is done in terms of how well the predicted agrees with the actual, expressed as correlation and standard error of estimate. For example, the stepwise regression program found 12 variables from the 42 history, physical and electrocardiogram variables (sets I and II) that were jointly predictive of the EF. The (multiple) correlation of the prediction based on these 12 variables with the actual EF was 0.87. The standard error of estimate was 10.5%. This implies that if these

TABLE III Ability of Sets of Noninvasive Variables to Predict Angiographic Measures

Variable Set	Number Vessels		Ejection Fraction		Coronary Status	
	MultR*	SEE†	MultR	SEE	MultR	SEE
Group I patients from USC-LAC hospital						
1–42 history, physical, electrocardiogram	0.93	0.56	0.87	10.5	0.93	0.46
1–48 including roentgenogram	0.96	0.47	0.91	9.5	0.95	0.43
1–55 including exercise test	0.99	0.26	0.94	8.0	0.96	0.39
1–63 including echocardiogram	0.99	0.30	0.95	7.7	0.98	0.29
All Group I and Group II patients						
1–42 history, physical, electrocardiogram	0.71	0.94	0.77	12.5	0.74	0.70

* Correlation of prediction from the set of noninvasive measures with the observed angiographic measure.
† Standard error of estimate; deviation of predicted measure from the observed angiographic measure.
USC-LAC = University of Southern California–Los Angeles County.

TABLE IV Performance of Estimated Coronary Status (CS) as an Indication for Angiography: Distribution of 169 Patients with Respect to Estimated and Actual CS

Estimated CS (Noninvasive)		Actual CS (Angiographic)			
CS Interval	Angiogram	No Surgery (CS > −0.5)	Surgery (CS < −0.5)	Total	% Agreement
Cutpoint: estimated CS = 0					
1.5–2.0	No	1*	0	1	100
1.0–1.5	No	13*	0	13	100
0.5–1.0	No	27*	1	28	96
0.0–0.5	No	41*	5	46	89
−0.5–0.0	Yes	18	17*	35	49
−1.0–−0.5	Yes	11	15*	26	58
−1.5–−1.0	Yes	3	12*	15	80
−2.0–−1.5	Yes	0	4*	4	100
−2.5–−2.0	Yes	0	1*	1	100
>0	No	82*	6	88	93
<0	Yes	32	40*	81	60
Total		114	55	169	78
	Sensitivity	...	89%	...	...
	Specificity	72%	...	...	...
Cutpoint: estimated CS = 0.12					
>0.12	No	72*	1	73	99
<0.12	Yes	42	54*	96	56
Total		114	55	169	75
	Sensitivity	...	98%	...	...
	Specificity	63%	...	...	...

* Patients correctly classified by noninvasive estimate of CS.

12 variables were used to predict an EF, for example, 65%, then about two-thirds of the time an angiogram would yield an actual value from 65 − 10.5 to 65 + 10.5, and 95% of the time from 65 − 21 to 65 + 21. Figure 2 displays how well the predicted EF agrees with the actual EF. In general, increasing the number of test sets increased the correlation and decreased the standard error of the estimate. An exception to this was for NV, since adding the echocardiographic measurements was not recognized as providing additional information.

The above analysis was based on only the 60 Group I patients, but with a large number of variables. As a result, the method was too optimistic. Using clinical variables alone, this model was applied to all 169 patients from both groups. Table III shows a considerable reduction in correlation and an increase in standard error of estimate.

The upper part of Table IV shows the performance of the estimated CS which, when <0, is taken as indicating angiography. At this cutpoint, there were 82 + 49 (78%) patients correctly assigned, with a sensitivity of 89% (95% confidence limits 78 to 96%) and a specificity of 72% (95% confidence limits 63 to 80%). Estimated CS, when high or low, is quite definitive, but reaches its nadir of agreement near −0.5.

Sensitivity and specificity can be adjusted as a function of the cutpoint. In this case, a higher sensitivity was found. The lower part of Table IV shows the performance of the estimated CS which, when <0.12, is taken as indicating angiography. At this cutpoint, there were 72 + 54 (75%) patients correctly assigned, with a sensitivity of 98% (95% confidence limits 90 to 100%) and a specificity of 63% (95% confidence limits 53 to 73%).

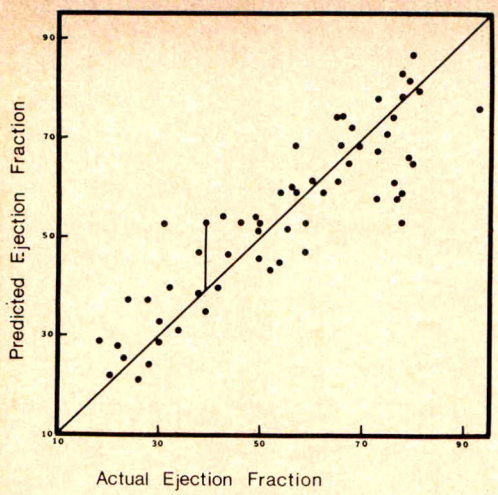

FIGURE 2. Actual and predicted ejection fraction based on significant history, physical, and electrocardiographic variables. The vertical line shows the deviation of the predicted from the actual for 1 patient.

TABLE V Example of Estimating Coronary Status From Clinical Data of a Patient

Clinical Variable	Patient Code	Coefficient
(constant)		−0.905
1 Age	45	−0.011
2 Sex	1	0.588
5 Number of myocardial infarctions	3	−0.198
7 Angina	0	−0.208
10 Smoker	1	−0.340
11 Diabetic	0	−0.623
12 Digitalis	1	−0.233
16 Edema	0	0.714
18 Ponderal index*	0.0265	19.334
19 Systolic blood pressure	135	0.008
25 S_3	1	−0.786
29 Anterior infarct	0	−0.755
32 Inferior infarct	1	−0.487
38 Right atrial enlargement	0	−0.697
41 Premature ventricular beat	0	−0.427

Estimated coronary status = −1.66.
* Weight/(height × height) = 145/(74 × 74).

Table V is an example of how the estimated CS was calculated. The variables involved, a patient's values and the regression coefficients are shown. Estimated CS = −1.66 was computed by multiplying each value by the corresponding coefficient, summing up and adding the constant. The actual CS was close to this, since actual EF = 30% and actual NV = 3.

Discussion

This review was a feasibility study of a small number of highly selected patients done by retrospective chart review. Thus, the generality of the results is limited. Patients with findings of valvular disease or congenital abnormalities were excluded. Those included had chest pain suggestive of angina pectoris or congestive heart failure unrelated to valvular disease. In Table V, some of the coefficients are more of a reflection of our particular sample, rather than representing a more general population. Edema, ponderal index and systolic blood pressure were positively related to CS; the higher they were, the better the CS. For example, the anomalous edema coefficient may have been a consequence of having several patients with congestive cardiomyopathy. Their high edema measurement would be correlated with a low NV despite a low EF, so their CS would be higher than that in patients with low edema measurement. Other variables of the 42 candidates may not have been included if they did not contribute added and significant information. The reader is not encouraged to use this model to make patient decisions for a different population.

Angiograms had been done to evaluate the patients as candidates for aortocoronary bypass graft surgery or aneurysm resection. Recent reviews[14] evaluating patients for bypass surgery have used symptoms and angiographic findings as the basis for the surgical decision. Of interest here are ventricular function, location of diseased vessels and NV. Surgery was not recommended in patients with severe nonreversible ventricular dysfunction. Patients with symptoms, 3-vessel disease and moderate impairment of ventricular function were regarded as good surgical candidates. The clinician was required to evaluate symptoms as well as coronary anatomy and ventricular function.

Currently the physician starts with clinical variables—history, physical examination and electrocardiogram. At this point, he or she could decide on angiography or opt for more information from noninvasive tests. Those most extensively studied have been chest film and exercise, usually including ST-segment change during a treadmill stress test. Echocardiography and radionuclide procedures have been recently introduced. The data used in this study were gathered before the radionuclide procedures were available to us, so none were reported here. Use of noninvasive tests as a predictor of coronary disease has evolved from case reports to much more extensive analysis in the past decade. The ultimate end points have been mortality and morbidity or, more positively, the length and quality of life. As angiography progressed, noninvasive testing was used to predict the angiographic results and then combined with them to predict mortality and morbidity. Inevitably, many noninvasive variables were combined into a single index as a basis for prediction,[15–17] as we have done here in defining CS.

Statistical analysis has progressed in concert with the type of data gathered. Contingency tables and chi-square tests were used to describe risk factors and end points, most often grouped as presence or absence.[18–20] For survival data, life tables and Cox analysis were used.[8,15–17,21,22] Discriminant analysis was used to find how to combine the noninvasive measures into a single index predictive of the presence of disease.[2,23] These measures can be either continuous, as age, or discrete, as sex. Disease is ordinarily taken as a dichotomy, that is, absent, or present if there is a coronary stenosis of ≥50% in at least 1 vessel. Stepwise discriminant analysis is a fairly efficient method of selecting the set of most promising variables and discarding those that do not add substantive and independent information.[15,24]

Concepts of test evaluation common in clinical laboratory practice[25] can be used to evaluate noninvasive testing. Sensitivity is the percentage of test results that are above a disease threshold, that is, positive, from a population of whom all are diseased. More explicitly, this can be called technical sensitivity. Specificity is the percentage of test results that are below a disease threshold, that is, negative, from a population of whom none are diseased. More explicitly, this can be called technical specificity. Using 0.12 as the cutpoint in our estimated CS test, these were 98% and 63%, respectively. Diagnostic sensitivity is the percentage of patients who indeed have the disease from a population of whom all had a positive test result. This is also often called the predictive accuracy.[26] Diagnostic specificity is the percentage of patients who indeed do not have the disease from a population of whom all had a negative test result. In the same estimated CS test, these were 99% and 56%, respectively.

Technical sensitivity and technical specificity are properties of the test. On the other hand, diagnostic sensitivity and diagnostic specificity are a consequence not only of the test, but also of the prevalence of the disease in the presenting population.[4] The calculus of these relationships are well known.[4] Receiver-operator characteristic curves are used to express the tradeoffs between diagnostic sensitivity and diagnostic specificity for a given disease prevalence.[6] The cost-effectiveness of test combinations in these terms and the application of information theory is of considerable interest.[5,6] These concepts have been used to show the value of a testing procedure. For the most part, they are not used to quantify the performance of the test when applied to an individual patient. The likelihood of the patient having the disease is, of course, dependent on the test result. The uncertainty decreases toward the more extreme values of CS (Table IV).

The decision to operate is based not only on the knowledge of coronary anatomy, but also on the evaluation of ventricular function. At the bedside, the clinician can frequently detect abnormal heart sounds or evidence of cardiac enlargement. Bruce[27] showed that cardiomegaly plus markedly impaired functional capacity on the treadmill or reduced blood pressure response to exercise can both help to identify severe ventricular dysfunction. These results were derived from patients with established ventricular disease; not included were patients for whom the clinician was unsure of this diagnosis.

Treadmill exercise testing and echocardiographic measurement and radionuclide studies have shown good correlations with angiographic results, although appreciable scatter is present. A more comprehensive combination of these with more conventional clinical variables still must be done.[3,28]

The most promising approach will be not only the incorporation of these more "exotic" tests, but also the sequential use of many variables. These should be selected on the basis of balancing their cost with their incremental information. A variable easy to obtain, such as those in a history, should be included. An expensive test should be included if it provides an appreciable amount of additional information. Such choices may be implemented using decision theory.[29]

When data are gathered, they should be in continuous form to the extent feasible. For example, ST-segment depression should not be categorized as greater than a threshold or not; the amount should be recorded.[5] It is simplistic to dichotomize variables as normal, abnormal or disease–no disease. In this report we have fallen into this convention. However, it may be essential to dichotomize if, for example, a decision must be made for angiography or surgery.

The findings in this report must be viewed as demonstrating feasibility, rather than providing quantitative answers. Angiographic findings of EF, NV and CS can be estimated from clinical data with high significance. Noninvasive data provide even better estimates. We have not quantitated this improvement as well as is needed to support a cost/benefit analysis. There were appreciable decreases in correlations when the models developed for the small group were applied to the larger and more heterogeneous group. However, they were still quite significant. Clinical data alone were adequate as a basis for deciding angiography. Estimated CS can be viewed in the same way as a laboratory test. In this study, it had a high sensitivity and specificity.

More work must be done to validate these findings, to quantify the models, and to make them generally applicable. Improvement can be made with a wider cohort of patients at many institutions, introduction of more recent noninvasive tests (for example, radionuclide studies) and refinement of the statistical model. The results of others as well as our own are so promising that a more extensive effort should be made to provide the clinician with such a service.

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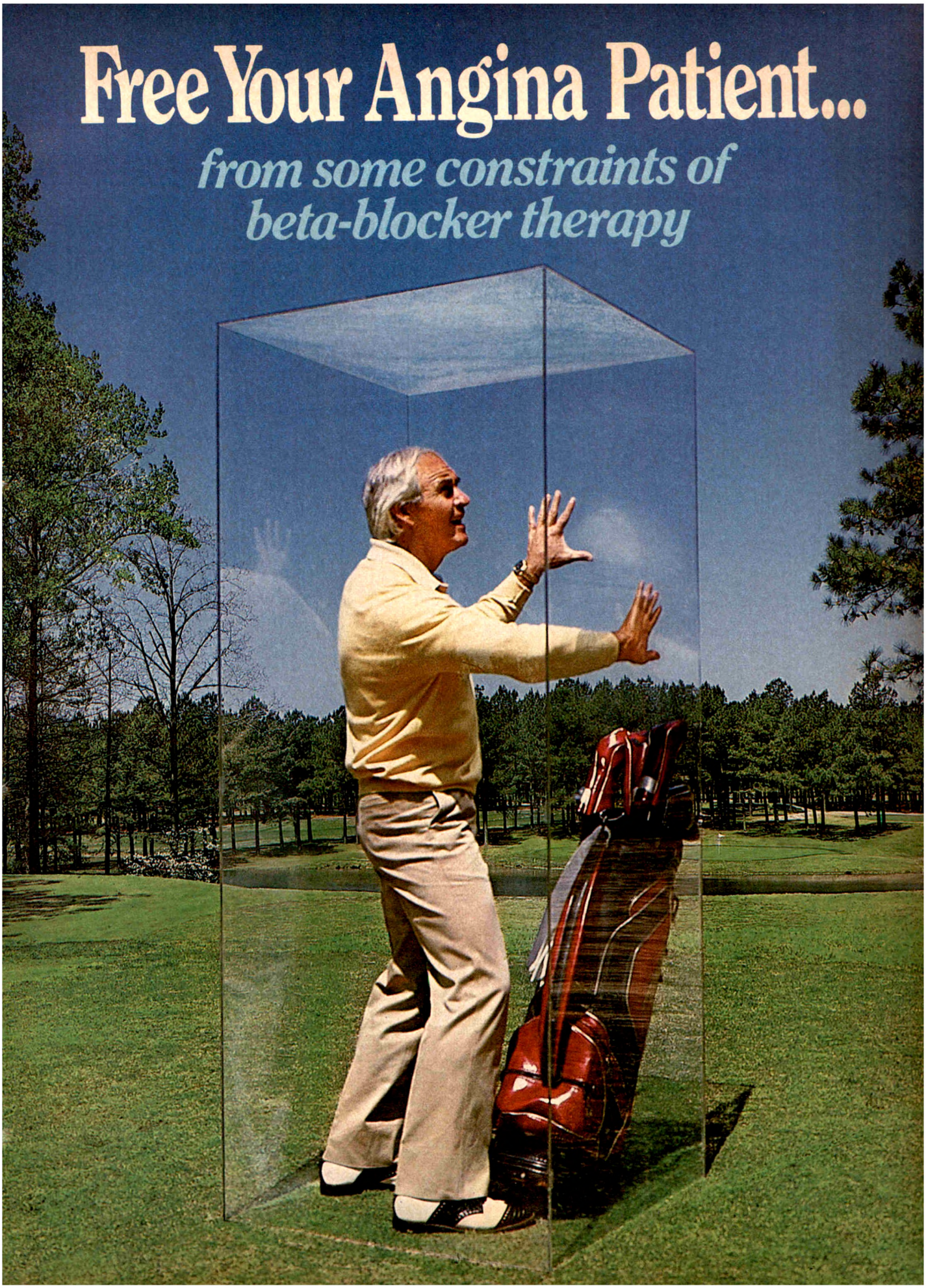
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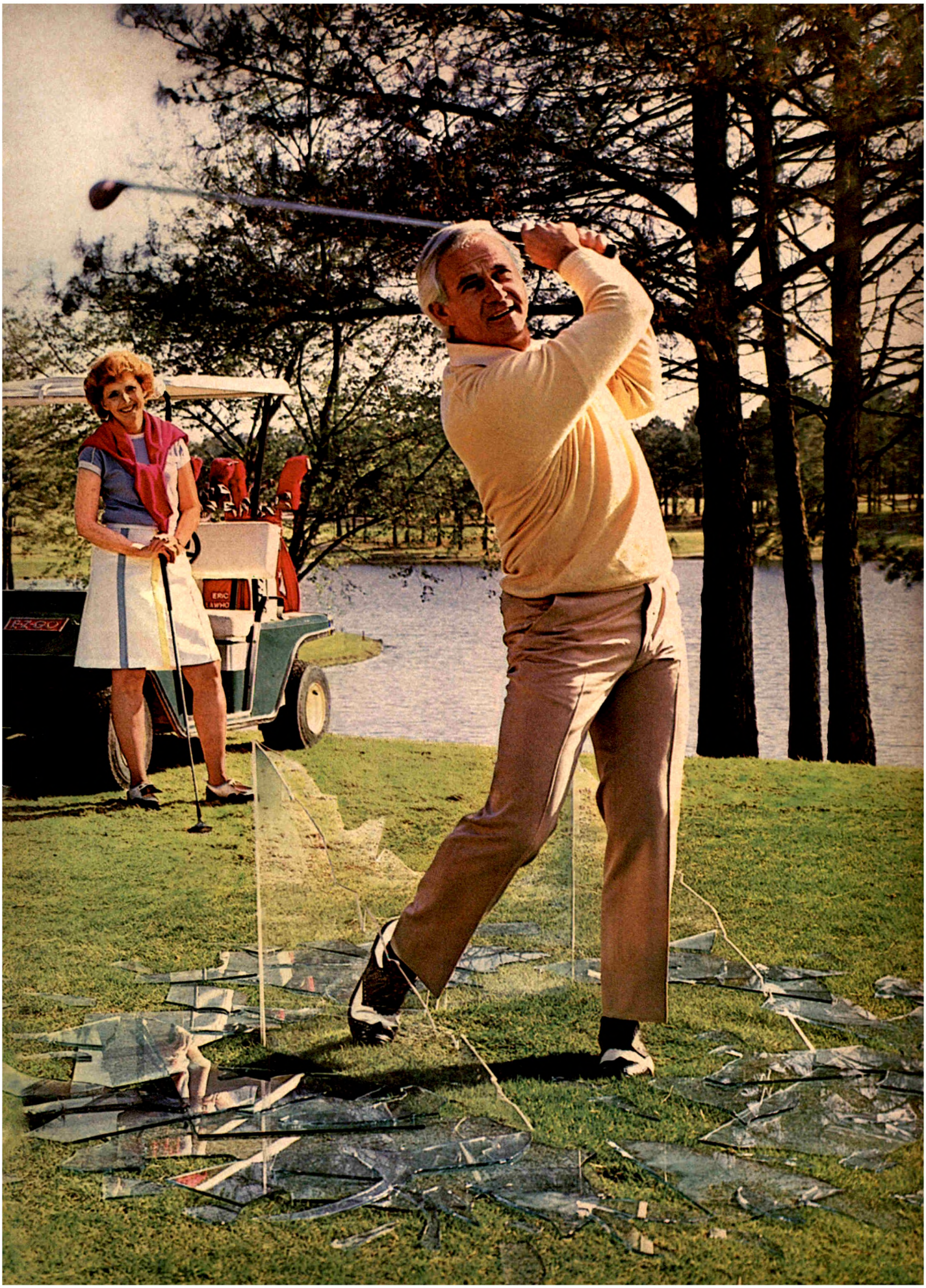

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Role of a Catheter Lead System for Transvenous Countershock and Pacing During Electrophysiologic Tests: An Assessment of the Usefulness of Catheter Shocks for Terminating Ventricular Tachyarrhythmias

LAWRENCE E. WASPE, MD, SOO G. KIM, MD, JEFFREY A. MATOS, MD, and JOHN D. FISHER, MD

The practicality and safety of using a single catheter system for transvenous countershock, programmed stimulation and ventricular pacing during electrophysiologic tests were evaluated in 13 patients with inducible sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). The efficacy and patient toleration of transvenous countershock were compared with other methods of arrhythmia termination. The same lead was used for programmed stimulation at the right ventricular apex and for VT termination by pacing methods during serial testing (20 ± 15 days [mean ± standard deviation]). Synchronized countershock using energies that patients found tolerable (0.01 to 5 J) terminated 31 of 50 episodes (62%) of induced VT. Episodes of VT cardioverted with these low energies were distinguished from other episodes by a longer cycle length (352 ± 62 ms versus 297 ± 50 ms, $p < 0.004$). Among paired episodes of VT matched for patient, date of induction, morphologic characteristics, cycle length and drugs administered, pacing methods (single extrastimuli and bursts of rapid pacing) were just as effective as low-energy countershock for VT termination (25 of 25 versus 21 of 25, difference not significant). Transvenous countershock was uniformly effective for termination of ventricular flutter and VF when sufficient energy was used (range 5 to 30 J, mean 20.4 ± 7.7). This required interfacing leads to a defibrillation unit. VT acceleration occurred during 7 of 50 synchronized low-energy cardioversion attempts (14%). There was no evidence of myocardial injury as a result of shocks as high as 30 J, but patients required increasing sedation when energy exceeded 0.5 J.

Thus, a single catheter system can be used for programmed stimulation, ventricular pacing and countershock during electrophysiologic tests. Low-energy countershock (0.01 to 5 J) is no more effective than pacing methods for VT termination and is tolerated less well. The most practical use of this catheter system, including any implantable unit, may be for slightly higher energy (5 to 30 J) countershock termination of repeated episodes of very rapid VT or VF, in which pacing techniques are ineffective. This method may be safer and less traumatic than conventional transthoracic countershock.

(Am J Cardiol 1983;52:477–484)

A variety of techniques for terminating ventricular tachyarrhythmias are available or under investigation.[1–16] Pacing techniques are well-tolerated by patients, but are frequently ineffective for rapid ventricular tachycardia (VT) and useless for ventricular fibrillation (VF).[1–7] External countershock is effective for the termination of ventricular tachyarrhythmias, but is traumatic and may result in skin burns or injury to the myocardium.[17,18] An alternative method of tachycardia termination that is more reliable than pacing, less traumatic than conventional countershock, and suitable for implantation would clearly be desirable.

For more than a decade, the feasibility of using intracardiac shocks to terminate ventricular tachyarrhythmias has been known.[12–14] This has resulted in the development of an effective automatic implantable defibrillator that delivers 25-Joule (J) shocks.[15,16] Re-

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TABLE I Patient Data

Pt	Age (yr)	MI	LV AN	EF (%)	Heart Size*	Anode Position†	Catheter Duration (days)	Clinical Arrhythmia	Previous Cardioversions	VT Episodes in Which TVCV (0.01 to 5 J) Was Attempted (n = 50)	VFL/VF Episodes in Which TVCV (5–30 J) Was Attempted (n = 17)
1	48	+	0	48	↑	RA	35	VF	1	0	1 (VFL)
2	72	+	+	45	N	SVC	14	VF	1	2	0
3	65	+	+	29	↑	SVC	45	VT	3	8	4 (VFL, 3 VF)
4	53	+	+	55	N	SVC	14	SUO	0	0	3 (VF)
5	56	+	0	40	N	RA	1,3,18‡	VF	1	1	1 (VF)
6	55	+	0	45	↑	RA	40	SUO	0	8	1 (VF)
7	61	0	0	49	↑	RA	41	NSVT	0	8	6 (VF)
8	50	+	0	. . .	↑	RA	13	VT	1	3	0
9	68	+	+	31	↑	RA	35	VT	4	13	0
10	55	+	0	45	N	SVC	5	VT	2	2	0
11	57	+	+	27	↑	RA	13	VF	1	1	0
12	49	+	+	30	↑	RA	21	VT	1	3	0
13	52	+	0	37	↑	SVC	6	VT	2	1	1 (VF)

* Determined by cardiothoracic ratio on chest X-ray (>0.5 = enlarged).
† Proximal pair of catheter electrodes.
‡ Patient 5 had 3 catheters inserted during serial electrophysiologic studies.
AN = aneurysm; EF = ejection fraction; LV = left ventricular; MI = previous myocardial infarction; N = normal; NSVT = nonsustained ventricular tachycardia; Pt = Patient; RA = right atrium; SUO = syncope of undetermined origin; SVC = superior vena cava; TVCV = transvenous cardioversion; VF = ventricular fibrillation; VFL = ventricular flutter; VT = sustained ventricular tachycardia; + = present; 0 = absent; ↑ = enlarged.

cently, lower energies delivered through an intravascular electrode catheter have been used safely in dogs and patients to terminate spontaneous and laboratory-induced VT.[8–11]

In the present study we assessed the role of an intravascular electrode catheter in the electrophysiology laboratory. We evaluated the safety, efficacy and practicality of using a catheter lead system for low-energy countershock, programmed ventricular stimulation and pacing termination of VT in patients with inducible sustained ventricular tachyarrhythmias. In addition, we evaluated patient tolerance of low-energy transvenous countershock and determined the comparative effectiveness of this method and pacing techniques for terminating episodes of induced VT with matched characteristics.

Methods

Patients (Table I): Patients were referred to the Arrhythmia Service at the Montefiore Medical Center for electrophysiologic evaluation of recurrent symptomatic ventricular tachyarrhythmias or syncope of undetermined origin. There were 12 men and 1 woman, aged 48 to 72 years (mean 57). Six patients had a history of recurrent sustained VT. Four patients had had cardiac arrests, and VF was documented at the time of resuscitation. One patient had recurrent episodes of nonsustained VT and 2 patients had episodes of syncope without a documented cause. Patients had experienced 1 to 10 occurrences of clinical arrhythmias before presentation. Ten patients had required conventional transthoracic countershock on 1 to 4 occasions.

All patients had coronary heart disease and 11 had had 1 or more remote myocardial infarctions. A left ventricular aneurysm was present in 5 patients. Cardiac surgery had been performed in 4 patients before referral for arrhythmia evaluation. Three patients had undergone coronary artery bypass grafting, and 1 patient had coronary artery bypass grafting and aneurysmectomy for symptoms of heart failure. Heart size was normal in 4 patients, whereas 9 patients had evidence of cardiomegaly on the basis of chest radiographs that demonstrated cardiothoracic ratios >0.50. Left ventricular ejection fraction determined by angiographic catheterization or gated radionuclide ventriculography ranged from 27 to 55% (mean 40 ± 9).

Approval to use a transvenously positioned catheter for internal cardioversion was obtained from the institutional review board of the Medical Center before recruitment of patients for this study. All patients gave written informed consent.

Catheter and system for transvenous countershock: The temporary electrode catheter used for internal countershock is a No. 9.5 Fr tripolar polyurethane insulated lead (Medtronic model 6880) (Fig. 1). The lead has 4 large, stain-

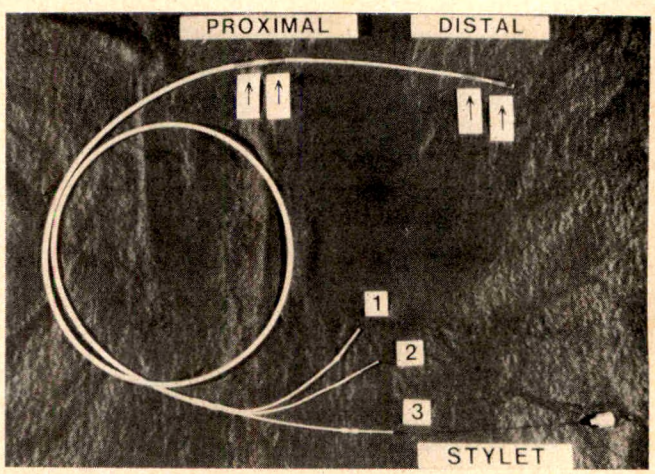

FIGURE 1. Catheter lead. **Arrows** point to stainless-steel electrodes. The distal pair are positioned at the right ventricular apex; the proximal pair are electrically common and lie in the right atrium or superior vena cava. 1, 2 and 3 refer to connector pins to the distal (ventricular) electrodes and the proximal common electrode. A stylet can be inserted into the catheter through connector pin 3 to aid in lead positioning. See text.

less-steel electrodes, each with a surface area of 1.25 cm^2. The distal pair of electrodes are located at the catheter tip and are separated by a 5-mm distance. The other pair of electrodes are separated by 5 mm, but form a single pole, and are located 100 mm proximal to the distal pair. Each electrode is connected to a separate conductor coil that terminates on 1 of 3 connector pins at the proximal end of the catheter. Catheter electrode spacing is designed so that positioning the distal pair in the right ventricular apex places the proximal common electrodes in the high right atrium or superior vena cava. The distal (ventricular) electrodes are used for electrogram sensing and can be used for bipolar ventricular pacing. During cardioversion or defibrillation, the distal electrodes are made electrically common, and form the cathode. The proximal common electrodes become the anode.

The catheter was inserted into the left subclavian vein using a percutaneous introducer technique and advanced under fluoroscopic guidance to the right ventricular apex. A stylet could be inserted into the lumen of the innermost conductor coil through 1 of the connector pins to stiffen the catheter sufficiently for positioning in the heart. Lead stability was verified by a chest radiograph within 24 hours of insertion and confirmed on subsequent days by fluoroscopy in the catheterization laboratory.

The catheter was connected to a battery-powered cardioverting device (Medtronic model 2342), which delivered a truncated exponential wave form, 5.5 ms in duration, at 10 energy levels ranging from 0.01 to 5.0 J. This cardioverting unit functioned in either a synchronous or asynchronous mode. When operating synchronously, an output pulse occurred at the first sensed electrical event after the discharge control was pressed. Sensing was performed by an amplifier in the unit that had a refractory period of 220 ms and a sensitivity continuously variable from 0.5 to 20 mV. The timing of synchronous pulses was verified by a sense marker signal (6 to 9 V, 5 ms in duration) before countershocks. When the asynchronous mode was selected, pressure on the discharge control produced an immediate output.

By means of terminals and switchbox contructed in cooperation with the Biomedical Engineering Department of the Medical Center, the cardioverting lead was connected simultaneously to a standard defibrillation unit (Physio-Control Lifepak 911). With this design, synchronous or asynchronous shocks could be delivered at higher energy levels (10 to 30 J) when needed. A Devices/Digitimer 4279 programmable stimulator and a Medtronic 5320 pulse generator were interfaced to the catheter's distal electrode pair through terminals on the cardioverting unit, permitting use of the cardioverting lead for programmed stimulation and ventricular pacing.

Study protocol: Patients became candidates for cardioverting lead insertion if sustained VT or VF was reproducibly initiated during a routine initial electrophysiologic study, using standard programmed stimulation techniques.[19] Briefly, initial electrophysiologic studies involved the insertion of 2 multipolar electrode catheters with the use of a percutaneous introducer technique into the subclavian and femoral veins. One catheter was positioned in the right ventricular apex and the other across the tricuspid valve to record the His bundle potential. Pacing was performed by means of a Devices/Digitimer 4279 programmable stimulator using stimuli 1 ms in duration at 4 times diastolic threshold. Ventricular arrhythmias were initiated by scanning diastole with 1, 2 or 3 ventricular extrastimuli during sinus rhythm or ventricular pacing at cycle lengths of 600 to 425 ms. If extrastimuli failed to induce ventricular tachyarrhythmias, bursts of rapid ventricular pacing were tried (10 to 20 beats) at cycle lengths of 500 to 240 ms. No patient in the study required stimulation at other right ventricular sites, isoproterenol infusion or left ventricular stimulation in order to initiate ventricular tachyarrhythmias. The arrhythmias induced reproduced arrhythmia morphologies and symptoms that had been documented clinically.

After induction of sustained VT or VF, the multipolar ventricular catheter was replaced with a cardioverting lead in the electrophysiology laboratory. Most often this replacement was performed the day of the initial electrophysiologic evaluation. Once positioned, the lead was used for programmed stimulation, pacing and transvenous countershock in the course of serial antiarrhythmic drug evaluation.

On initiation of sustained VT, output energies of 0.01, 0.05, 0.10, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, and 5.0 J were delivered in the synchronous mode in attempts to restore sinus rhythm. Efforts were made to deliver shocks in an incremental fashion until successful conversion to sinus rhythm occurred. However, when VT was not well-tolerated or resulted in hemodynamic instability, the higher energies in this range were initially and subsequently selected in attempts to terminate arrhythmias quickly. To avoid the reported possibilities of VT acceleration or precipitation of VF, transvenous shocks were administered synchronously only when synchronization occurred within the first 80% of the surface QRS interval.[8,9,11] If cardioversion attempts failed with synchronized output energies of $\leq$5 J or ventricular flutter/fibrillation occurred, arrhythmia conversions were attempted through the catheter with asynchronous shocks of 5 J or with synchronous or asynchronous shocks of 10 to 30 J delivered from the interfaced standard defibrillation unit (Physio-Control Lifepak 911). A second defibrillation unit was available (Electronics for Medicine model ISD) in case backup transthoracic shocks were needed. Patients were sedated with 2 to 10 mg of intravenous diazepam if discomfort occurred during incremental attempts at cardioversion.

Cardioverting leads were used in 8 patients who gave informed consent, to compare the efficacy of synchronized transvenous countershock (0.01 to 5 J) with that of pacing techniques for terminating laboratory-induced VT. Pacing methods used to terminate VT included scanning diastole with a single extrastimulus and rapid pacing at cycle lengths of 400 to 220 ms for 5 to 10 seconds. Countershock and pacing methods were alternately used in attempts to terminate paired episodes of VT, which were matched for patient, cycle length, morphologic characteristics, antiarrhythmic drugs administered and day of induction.

During electrophysiologic studies, VT was defined as sustained if it persisted for >15 seconds or required termination in less time because of hemodynamic compromise. Catheter shocks of 0.01 to 5 J, delivered from the cardioverting device, were defined as *low-energy* transvenous countershocks. Shocks of 10 to 30 J, which required use of the interfaced defibrillation unit, were defined as *high-energy* transvenous countershocks. Recordings of ECG leads 1, 2, aVF, and V_1, intracardiac electrograms, and sense marker signals were displayed on the oscilloscope of an Electronics for Medicine physiologic recorder (DR-12 or VR-12) and simultaneously recorded on heat-sensitive paper or on an 8-channel Siemens-Elema Mingograf at paper speeds of 25 to 100 mm/s.

Serum creatine kinase activity was measured in 10 patients 24 hours after studies involving transvenous, but not transthoracic, countershocks, to evaluate the possibility of catheter shock-related myocardial injury. All creatine kinase determinations included an agarose gel electrophoresis assay (Beckman Paragon System) for B-subunit activity (myocardial isoenzyme). The values of total creatine kinase and B-subunit activity were considered elevated if the values exceeded the normal range (10 to 100 IU/liter and 4% of total creatine kinase activity, respectively).

TABLE II Analysis of Ventricular Tachycardia Termination Methods (50 Episodes)*

Patient	Synchronous Low-Energy TVCV: 0.01 to 5 J	Other Methods Required		
		High-Energy TVCV: 10 to 30 J	DCCV	RV
2	1 (370)†	...	1 (270)†,‡	..
3	0	3 sync (230–290) 3 async (240–300)§	2 (230, 310)‡	..
5	1 (270)	...	...	..
6	4 (340–350)	3 sync (290–370)	...	1 (37
7	5 (240–425)	1 sync (230) 2 async (270, 370)§	...	..
8	2 (370–465)	...	...	1 (31
9	12 (290–420)	...	...	1 (38
10	2 (230–240)	...	...	...
11	0	...	...	1 (27
12	3 (330–470)	...	...	...
13	1 (320)	...	...	...
Summary				
VT episodes	31	12	3	4
Range of VT cycle lengths (ms)	(230–470)	(230–370)	(230–310)	(270–3

* Low-energy (0.01 to 5 J) transvenous cardioversion (TVCV) was attempted during all 50 episodes of induced ventricular tachycardia synchronized, low-energy shocks were ineffective, patients became hemodynamically unstable, VT accelerated, or ventricular flutter/fib occurred, termination was achieved by other methods: rapid ventricular pacing (RVP), synchronous (sync) or asynchronous (async) tran shocks of 10 to 30 J, or transthoracic cardioversion (DCCV). See text for details.

VT episodes are organized according to patient and ultimate method of termination. Cycle lengths of the VT episodes in milliseconds are individually or as a range in parentheses.

† VT was accelerated by low-energy TVCV attempts. In 1 instance further low-energy TVCV attempts were successful. In the other, DC necessary.

‡ Catheter lead was not interfaced to a defibrillation unit, which would have permitted high-energy TVCV attempts.

§ Ventricular fibrillation was precipitated during low-energy TVCV attempts.

Statistical methods included the Student *t* test for paired and unpaired data, Fisher's exact test and McNemar's test for correlated proportions where appropriate. The Mann-Whitney nonparametric test was used to compare variables across 2 groups. Associations between 2 continuous variables were assessed using the Spearman rank-order correlation coefficient. Data are expressed as mean ± standard deviation. Results were considered statistically significant at $p < 0.05$.

Results

Lead insertions and programmed stimulation: Uncomplicated catheter insertions were carried out in the electrophysiology laboratory in 13 patients (Table I). Leads remained in stable position for 1 to 45 days (mean 20 ± 15 days). One patient required a total of 3 lead insertions (patient 5) due to interruption c trophysiologic studies by coronary artery bypass s in 1 instance and the occurrence of a catheter-r infection on another occasion, to be described. instances the catheter tip was positioned in the ventricular apex. In general, the proximal ca electrodes were located in the right atrium wh heart was enlarged, and in the superior vena cava the heart was normal in size (Table I, Fig. 2). At of lead insertion, initial pacing thresholds with a pulse duration ranged from 0.5 to 2.5 V (mean 1.2 Despite stable lead positions, thresholds increa as much as 10 V (mean 3.6 ± 3.3) from 1 to 3((mean 9 ± 11) after insertion. Nevertheless, ever was usable for programmed stimulation at the ventricular apex for as long as it remained in a pa Upon removal of the catheters, electrodes and insu materials were structurally intact.

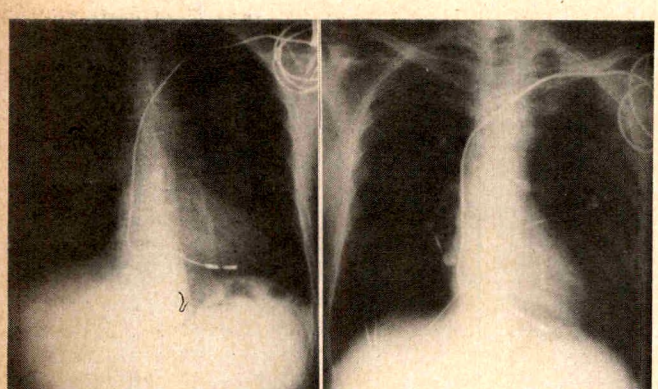

FIGURE 2. Chest radiographs illustrating typical catheter lead placements. **Left,** enlarged heart (Patient 1). The catheter tip is at the right ventricular apex and the proximal common electrode lies in the right atrium. **Right,** normal-sized heart (Patient 4). Positioning the catheter tip at the apex of the right ventricle places the proximal common electrode in the superior vena cava.

Ventricular tachycardia (Table II): During trophysiologic studies, synchronized low-energy to 5 J) transvenous shocks were used in efforts t minate 50 episodes of sustained VT induced in tients (1 to 13 episodes per patient) (Table I). VT lengths ranged from 230 to 470 ms (mean 331 During 47 of 50 episodes, patients were receivin ventional or experimental antiarrhythmic drugs (22 episodes) or in combinations (25 episodes cluding subthreshold attempts, a total of 160 syn nous shocks were delivered, terminating 31 episo induced VT (62%) (Fig. 3).

The remaining 19 episodes of VT required methods of termination. Seven episodes were t nated by *synchronized* transvenous shocks of l energy (10 to 30 J). During these episodes, patie

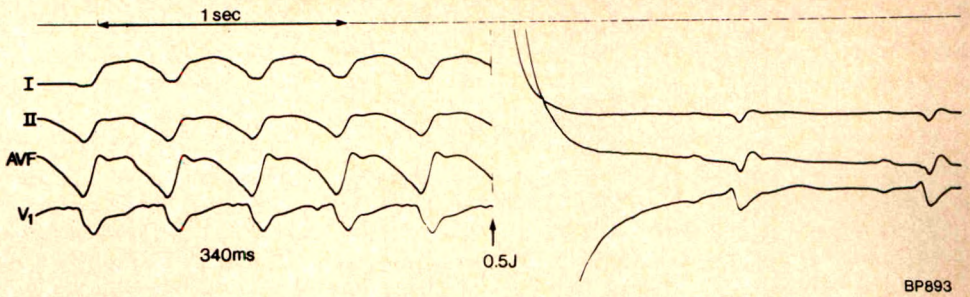

FIGURE 3. Patient 6—termination of ventricular tachycardia (cycle length 340 ms) using low-energy transvenous cardioversion. Scalar leads I, II, aVF and V_1 are displayed. A synchronized catheter shock of 0.5 J (**arrow**) restores sinus rhythm.

ther became hemodynamically unstable and syncopal in the course of unsuccessful low-energy cardioversion attempts or required heavy sedation (≤10 mg of intravenous diazepam) to tolerate intracardiac shocks of ≥10 J. In contrast, patients remained alert or required less sedation when cardioversion was accomplished with energies of 0.01 to 5 J. Five episodes of tachycardia were terminated with *asynchronous* transvenous shocks of 10 to 30 J, when VF occurred during low-energy cardioversion attempts. Four VT episodes were terminated by rapid pacing with the cardioverting lead. Three other episodes of VT were terminated by conventional transthoracic countershock after low-energy attempts failed. These episodes of VT were induced in 2 patients (patients 2 and 3) before catheter leads were routinely interfaced to a source of higher-energy transvenous shocks

Factors correlating with low-energy transvenous countershock efficacy: Episodes of VT terminated by synchronized shocks of 0.01 to 5 J had longer cycle lengths (352 ± 62 versus 297 ± 50 ms, $p < 0.004$ by the Mann-Whitney test) and were characterized by the administration of lower maximum energies during cardioversion attempts (1.40 ± 1.71 versus 3.42 ± 2.14 J, $p < 0.004$ by the Mann-Whitney test). Low-energy countershocks terminated 23 of 42 VT episodes with cycle lengths of 230 to 380 ms (Table II). However, efficacy was uniform (8 episodes) when cycle length exceeded 380 ms. In contrast, the timing of synchronization, expressed as an initial percentage of the surface QRS interval, did not distinguish between tachycardia episodes that were successfully and unsuccessfully treated with low-energy shocks (33 ± 16% versus 42 ± 28%, difference not significant [NS]). Similarly, the success or failure of transvenous cardioversion did not correlate with factors that characterized distal electrode contact with endocardium, such as catheter pacing threshold during programmed stimulation (4.8 ± 3.9 versus 2.4 ± 1.1 V, NS) or endocardial R-wave amplitude recorded during sinus rhythm (5.7 ± 3.1 versus 4.9 ± 1.6 mV, NS) or during VT (7.4 ± 8.5 versus 7.1 ± 0.8 mV, NS). In addition, the efficacy or inefficacy of low-energy countershock was not related to the duration of VT before the initial cardioversion attempt (43 ± 34 versus 34 ± 39 seconds, NS) or to the final attempt (71 ± 56 versus 66 ± 54 seconds, NS).

Among episodes of VT terminated by energies of 0.01 to 5 J, there was no correlation between the energy dose required and VT cycle length, timing of synchronization, pacing threshold, endocardial R-wave amplitude in sinus rhythm or VT, or arrhythmia duration before initial or final shocks. Correlation coefficients ranged from −0.32 to +0.28.

Comparison of ventricular tachycardia termination methods: During electrophysiologic studies, 25 paired episodes of VT were induced in 8 patients to compare the termination efficacy of low-energy transvenous countershock with that of pacing techniques (single extrastimuli and rapid pacing). These 25 paired episodes of VT were a subset of the total number in the study (50) subjected to attempted transvenous cardioversion. VT episodes were matched for patient, day of study, antiarrhythmic drug or drugs administered, morphologic characteristics and cycle length (230 to 465 ms, mean 342 ± 57). The method of termination first evaluated was randomly varied for each tachycardia pair. Among the paired episodes, transvenous countershock and pacing methods were comparably effective in terminating VT (21 of 25 versus 25 of 25 episodes, $p = 0.12$ by McNemar's test). Tachycardias terminated by low-energy shocks required an average of 1.53 ± 1.86 J, whereas matched episodes were converted to sinus rhythm by rapid ventricular pacing in 23 cases and single extrastimuli in 2. The cycle lengths of the 2 tachycardias terminated by single extrastimuli were well above the mean for all the pairs (400 and 465 ms). Cycle lengths ranged from 270 to 370 ms among the 4 episodes of VT not terminated by shocks of ≤5 J. Sinus rhythm was restored in 2 of these episodes by rapid pacing. The other episodes were terminated by high-energy (25 J) asynchronous transvenous countershock when VF occurred during termination attempts with synchronized shocks of 5J.

Ventricular flutter and ventricular fibrillation (Table I): In 7 patients, 2 episodes of ventricular flutter and 15 episodes of VF occurred in the course of electrophysiologic testing, whereas the catheter lead system was connected to deliver energies in excess of 5 J. Termination of VF was accomplished on every occasion with an asynchronous transvenous shock of 5 to 30 J (mean 20.4 ± 7.7) (Fig. 4B). Synchronized low-energy cardioversion of the episodes of ventricular flutter (cycle lengths 200 and 215 ms) could not be attempted because of the 220-ms refractory period of the sense amplifier in the cardioverting unit. These arrhythmias were terminated by asynchronous transvenous shocks of 12 and 10 J, respectively. Notably, asynchronous transvenous shocks did not fail to terminate any episode of ventric-

ular flutter or VF, which occurred while catheter leads were interfaced to a source of sufficient output energy (up to 30 J).

Creatine kinase measurements: Creatine kinase and creatine kinase B-subunit activity were measured as an index of possible myocardial injury, after 22 studies in 10 patients in which transvenous but not transthoracic shocks were administered. One to 13 (mean 4 ± 3) shocks of 0.01 to 30 J were administered during these studies, representing cumulative energy doses of 0.01 to 70.75 J (mean 21.68 ± 24.13). Creatine kinase activity measured 24 hours after transvenous shocks varied from 11 to 972 IU/liter, and 7 of the 22 values were elevated (120 to 972 IU/liter). Five of the elevated creatine kinase values were obtained after initial electrophysiologic studies, which were longer (4 to 6 hours) and involved the use of more electrode catheters (2 or 3) than the drug-evaluation studies that followed. Total countershock energies administered during initial electrophysiologic studies were lower, on the average, than those during drug evaluation studies (6.37 ± 10.68 versus 26.18 ± 25.32 J, $p < 0.003$). Despite some elevations in total creatine kinase activity, B-subunit activity was not increased in any determination. In addition, no patient developed persistent electrocardiographic changes after studies that involved transvenous cardioversion. These findings suggest that significant myocardial damage attributable to transvenous shocks probably did not occur. Elevations in total creatine kinase activity may have been related to tissue trauma during catheter insertions.[20]

Problems related to catheter use and transvenous countershocks: *Acceleration of VT:* During transvenous cardioversion attempts, synchronized shocks of 0.25 to 5 J accelerated VT or precipitated VF in 7 of 50 episodes (14%) of induced VT (Table II). VT acceleration occurred on 2 occasions in patient 2 after shocks of 0.25 J. In 1 instance, VT was accelerated from a cycle length of 370 to 340 ms and termination was achieved by a subsequent shock of 5 J. On the other occasion, VT was accelerated from a cycle length of 270 to 200 ms. This episode was terminated by transthoracic countershock. Synchronized shocks of 5 J percipitated VF on 5 occasions in patients 3 and 7 during attempts to terminate episodes of VT with cycle lengths of 240 to 370 ms (Fig. 4). In each instance, VF was terminated by an asynchronous transvenous shock of 15 to 30 J. Transvenous shocks that resulted in VT acceleration or VF were higher in energy than were those that did not (3.64 ± 2.32 versus 0.91 ± 1.41 J, $p < 0.001$). However, episodes of VT complicated by transvenous shock-induced acceleration or VF did not differ from other episodes with respect to cycle length (307 ± 45 versus 335 ± 65 ms, NS) or the timing of synchronization (36 ± 27% versus 36 ± 20% of the QRS interval, NS). In no instance of tachycardia acceleration or precipitation of VF had synchronization occurred after the initial 75% of the surface QRS interval.

Atrial arrhythmias: Because atrioventricular dissociation was often present during VT, catheter shocks were random in relation to atrial depolarization. Consequently, "synchronized" transvenous shocks of 0.10 to 5 J (mean 1.37 ± 1.71) initiated 2 atrial flutter episodes and 5 atrial fibrillation episodes in 7 of 47 episodes (15%) of VT, which were induced during a baseline of sinus rhythm. On all but 1 occasion, atrial arrhythmias were well tolerated and spontaneously reverted to sinus rhythm within 12 seconds to 2 hours. One episode of atrial fibrillation initiated in patient 9 was persistent and was associated with a ventricular response rate of 120. Prompt restoration of sinus rhythm was achieved in this instance by a transvenous shock of 5 J (Fig. 5).

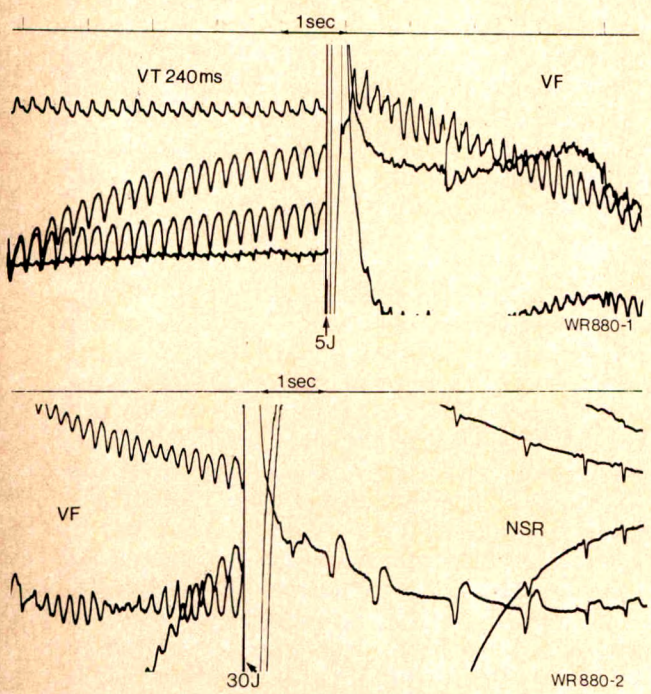

FIGURE 4. Top, Patient 3—surface lead recordings of ventricular tachycardia (VT) at a cycle length of 240 ms, which has been induced during electrophysiologic testing. Attempted cardioversion with a synchronized catheter shock of 5 J (**arrow**) produces ventricular fibrillation (VF). **Bottom,** same patient and tachyarrhythmia episode a few second later. An asynchronous transvenous shock of 30 J (**arrow**) terminates VF. Sinus rhythm (NSR) resumes after 5 complexes of a slow ventricular rhythm.

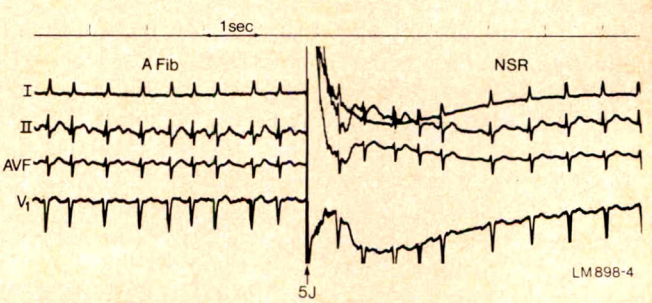

FIGURE 5. Patient 9—electrocardiographic recordings of atrial fibrillation (A Fib) with an average ventricular rate of 120, which occurred after termination of ventricular tachycardia by a synchronized transvenous shock of 1.5 J. A subsequent catheter shock of 5 J (**arrow**) restored normal sinus rhythm (NSR) after 4 complexes of an ectopic atrial rhythm.

Infection: Catheter-related infections occurred in 3 patients despite sterile precautions routinely observed during electrode catheter insertions and frequent dressing changes while leads remained in position. Patient 5 developed a cutaneous abscess over the insertion site after a catheter had been in place for 3 days. Patients 8 and 10 developed fever and bacteremia after leads had been in place for 12 and 5 days, respectively. In each case *Staphylococcus aureus* was cultured from an abscess or the blood. Neither patient with bacteremia had evidence of endocarditis, and all infections responded to catheter removal and 2 to 4 weeks of intravenous bacteriocidal antibiotics. After these infections (possibly related to the large surface area of the leads and to the electrostatic affinity of polyurethane insulation), sterile procedures were intensified to include use of a sterile mask during catheter insertion and more frequent dressing changes at the insertion site. Subsequently, no other catheter-related infections occurred.

Patient discomfort: Only shocks of ≤0.5 J were tolerated without discomfort. Patients experienced increasing discomfort when higher energies were given, and frequently requested or required sedation to tolerate countershocks >0.5 J. Nevertheless, patients who had experienced transthoracic countershock found transvenous shocks less unpleasant.

Discussion

Low-energy shocks delivered through an intravascular lead are reported to be safe and effective for terminating ventricular tachyarrhythmias that occur in a clinical setting or are induced by programmed electrical stimulation.[9–11] A system for transvenous countershock has potential advantages in situations of recurrent VT or VF, in which repeated high-energy transthoracic shocks might otherwise be necessary for arrhythmia termination.[9–11]

We assessed the safety, efficacy and patient toleration of transvenous countershock in the setting of the electrophysiology laboratory, where repeated inductions of ventricular tachyarrhythmias were expected, and compared the efficacy and patient toleration of this technique with those of other methods of arrhythmia termination. In addition, we evaluated the practicality of using a single catheter system for cardioversion and defibrillation, programmed ventricular stimulation and termination of VT by pacing methods during serial electrophysiologic testing.

Electrophysiologic testing: Catheter leads were usable for programmed stimulation at the right ventricular apex for as long as they remained in patients (up to 45 days). In addition, there were no difficulties in using leads to terminate induced VT with pacing methods on numerous occasions. We encountered no obvious lead displacements. However, the rapid increases in stimulation threshold we noted may have been related to subtle changes in distal electrode position that were not detectable on chest X-ray or fluoroscopy.

Cardioversion of ventricular tachycardia: In our study, 31 of 50 episodes (62%) of induced VT were terminated by synchronized transvenous shocks of 0.01 to 5 J. The average energy needed for these cardioversions (1.4 J) was usually tolerated by awake or mildly sedated patients. By using higher energies (10 to 30 J), an additional 7 episodes of VT were terminated, but the shocks were tolerated less well. Because conscious patients required heavy sedation before receiving intracardiac shocks of ≥10 J, high-energy transvenous cardioversion cannot be considered a preferred method for the *routine* termination of laboratory-induced VT.

When better tolerated energy levels (0.01 to 5 J) were used, transvenous countershock was unvaryingly successful only when VT cycle length exceeded 380 ms. Moreover, energy requirements for cardioversion bore no predictable relationship to tachycardia cycle length, to timing of synchronization or to indicators of catheter electrode contact with the right ventricular endocardium. Other factors not rigorously analyzed, such as antiarrhythmic drugs, heart size, and site of origin of VT in relation to lead position, may have influenced cardioversion energy requirements.[9,21]

Other investigators using similar catheter systems have reported higher incidences of VT termination with transvenous countershocks.[9,10] Zipes et al[9] terminated 47 of 49 episodes (96%) of VT using shocks of 0.025 to 2 J. Yee et al[10] found that shocks of 2.5 to 5 J terminated 12 of 16 episodes (75%) of recurrent VT in the setting of a coronary care unit. Their cardioversion rate improved to 95% (86 of 91 episodes) when energies of up to 10 J were used.[10] Differences in VT cycle length may explain the discrepancy between our results and those of Zipes et al.[9] Whereas 70% of VT episodes in the latter study[9] had a cycle length of ≥400 ms, only 7 episodes (14%) in the present study were as slow. Indeed, low-energy transvenous cardioversion was uniformly effective among our patients when VT cycle length exceeded 380 ms. VT cycle lengths were not described in the report of Yee et al[10] and, unlike the present study, most cardioversion attempts were with energies >5 J. When countershocks of ≤5 J were analyzed, the VT termination rate observed by Yee et al[10] (75%) was similar to that we found.

Previous work with catheter countershock systems demonstrated that optimal effectiveness was achieved when the distal electrode (cathode) was located at the right ventricular apex.[23] The position of the anode was less important, whether in the superior vena cava, right atrium or coronary sinus, as long as the electrode had an adequate surface area.[8,22] Because the catheter lead used in our study was designed and positioned on the basis of these considerations, the cardioversion rate we observed was probably representative of what is attainable with low energies (0.01 to 5 J).

Comparison of ventricular tachycardia termination methods: Among carefully paired episodes of laboratory-induced VT, we found no difference in rates of termination by low-energy (0.01 to 5 J) transvenous shocks and pacing methods (single extrastimuli and rapid ventricular pacing). Because paired episodes of VT were selected in that all were induced at the apex of the right ventricle, 1 of the methods of termination might have been superior in a series that included VT

induced from other right or left ventricular sites. However, the overall cardioversion rate we attained using shocks of up to 5 J (62%) was little different from the VT termination rates we[3,5] (89 to 95%) and others[2,6,7] (66 to 79%) observed using pacing methods to terminate many episodes of VT induced from several ventricular sites.

Furthermore, synchronized transvenous shocks caused VT acceleration more often than did pacing methods during attempted terminations of the paired arrhythmias (2 of 25 versus 0 of 25). When we analyzed our overall experience with methods of VT termination, intracardiac shock remained a more common cause of acceleration than pacing techniques[17] (7 of 50 episodes versus 22 of 573, $p < 0.006$ by Fisher's exact test). Thus, our data suggest that low-energy transvenous shocks are no more effective than pacing methods for VT termination, and may result in tachycardia acceleration more frequently.

Termination of ventricular flutter and ventricular fibrillation: In contrast to results during VT, transvenous countershocks were uniformly effective when used to terminate episodes of ventricular flutter and VF. Higher energies (5 to 30 J) were required to terminate these arrhythmias than most episodes of VT. Nevertheless, these energy doses were much smaller than what would have been needed for transthoracic defibrillation. Because many patients retain some level of consciousness during defibrillation attempts, transvenous countershock with relatively low energies is probably better tolerated than the alternative of transthoracic countershock.

Safety: The absence of electrocardiographic changes or elevations in creatine kinase B-subunit activity after intracardiac shocks suggests that transvenous countershocks caused no significant myocardial damage. Studies that have examined the effect of catheter shocks on the heart found that injury, when it occurred, was limited to very small areas of necrosis or endocardial hemorrhage in the region of catheter electrodes.[10,23] Because our patients and those in these studies[10,23] received similar shock energies, evidence is strong that multiple transvenous shocks at energies as high as 30 to 50 J result in little myocardial injury.

Implications: We conclude that a single catheter lead system can be used for countershock and ventricular pacing during serial electrophysiologic testing. The most practical use of a catheter system for internal countershock may be for relatively low-energy conversions (≤30 J) of repeated episodes of rapid VT or VF, in which pacing techniques are ineffective. Future systems, including implantable units, may be very useful if energy requirements for VT termination can be decreased (less discomfort), but should be capable of delivering sufficient energy to terminate accelerating VT or VF.

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Significance of Prolonged Electrocardiographic Pauses in Sinoatrial Disease: Sick Sinus Syndrome

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Eighty-four patients (2.6%) were found to have prolonged (≥2.0 seconds) sinoatrial pauses in a review of 3,259 consecutive patients who had 24-hour Holter electrocardiographic studies. Pauses averaged 2.6 ± 1.5 seconds (± standard deviation) (range 2.0–15.2). In 17 (20%), no underlying heart disease was found and in 8 (10%), prolonged pauses appeared to be drug-induced. No relation was found between length of pauses and presence of symptoms or risk of death. Twenty patients received a pacemaker. Pacemaker recipients were older and more likely to be male and to have symptoms, although 7 were asymptomatic. Patients who received a permanent pacemaker were not different from nonrecipients with respect to average longest pause, mechanisms of pause, underlying heart condition or average time of follow-up. However, the survival rate was not improved by permanent pacemaker implantation. Of the 17 patients who died, only 3 died of cardiac causes; none had a recognizable bradycardic cause. Thirteen who initially had syncope did not receive a pacemaker; 2 died of noncardiac causes and none had a subsequent syncopal episode. Ten patients with a syncopal episode received a permanent pacemaker; 3 subsequently died and 3 survivors continued to complain of dizziness. Of the 37 patients who did not have any symptoms on initial examination, only one subsequently had a syncopal episode. Thus, length of sinoatrial pauses correlates poorly with symptoms and does not predict sudden death. Unless prolonged sinoatrial pauses are shown to cause symptoms, such pauses per se are not an indication for permanent pacemaker implantation.

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Disorders of sinoatrial function are the leading indication for pacemaker implantation.[1–3] Although a pacemaker would be expected to relieve symptoms caused by bradycardia, there is no evidence that life is prolonged by pacemakers implanted for sinoatrial bradycardia, even in patients with symptoms.[4–6] However, the occurrence of such bradyarrhythmias has been viewed as premonitory for Stokes-Adams attacks or even sudden death. Because of these concerns, the presence of prolonged sinoatrial pauses, even in patients without symptoms, has been suggested as an indication for pacemaker implantation.[7] Accordingly, to determine the prevalence, significance and natural history of patients with prolonged (≥2.0 seconds) sinoatrial pauses, 24-hour Holter recordings that had been analyzed at The Brooklyn Hospital were reviewed to identify patients with this condition.

Methods

Twenty-four-hour Holter recordings done at The Brooklyn Hospital between 1977 and 1981 in 3,259 consecutive patients were reviewed. Eighty-four patients (2.6%) were found to have sinoatrial pauses ≥2 seconds. In 82, clinical data at the time of the Holter study were available and in 80 of these patients, follow-up information was obtained. Twenty patients received a pacemaker; in 19, it was inserted during the same hospitalization that the Holter study was done.

Patients with electrocardiographic abnormalities were grouped as follows: Group I had sinoatrial node dysfunction (sinus bradycardia, sinoatrial block or sinus arrest). Group II had bradytachycardia syndrome with pauses upon termination of episodes of tachycardia, during tachycardia or independent of episodes of tachycardia. Group III had chronic atrial fibrillation with a slow ventricular response. Table I shows the distribution of patients into these groups.

Follow-up data were obtained from patients, relatives, private physicians and medical records. The survival rate was determined using life-table methods[8] and the differences between patients who received a pacemaker and those who did not were compared using a chi-square corrected for continuity.[9] A p value <0.05 was considered significant. Values are expressed as mean ± standard deviation.

Results

Clinical data: The patients were 30 to 104 years (average 72 ± 13). Forty-one patients were male and 43 were female. Patients who received pacemakers were older ($p < 0.05$), had a higher male distribution (chi-square = 4.7, $p < 0.05$) and were more likely to be symptomatic (Table II). There were no differences between these groups in the electrocardiographic mechanisms of pause, the underlying cardiac conditions or associated medical problems, with the exception that no patient with cancer received a pacemaker.

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TABLE I Mechanisms of Pause*

	Pacemaker Group		No Pacemaker Group	
Sinoatrial node dysfunction	5 (25%)		22 (34%)	
Bradytachycardia syndrome	8 (40%)		25 (39%)	
After tachycardia		2		5
During episodes of atrial flutter or fibrillation		1		8
Marked sinus bradycardia or arrest independent of episodes of tachycardia		8		11
Chronic atrial fibrillation with slow ventricular rate	7 (35%)		17 (27%)	
Total	20		64	

* Some patients had more than 1 mechanism.

TABLE II Salient Clinical Features

Clinical Data	Pacemaker Group	No Pacemaker Group
Age (yr) (mean ± SD)	78 ± 8*	71 ± 14
Male:female	14:6*	27:37
Underlying cardiac condition		
Coronary artery disease	8	17
Hypertensive cardiovascular disease	4	12
Valvular heart disease	1	7
Congestive (dilated) cardiomyopathy	0	3
Heart failure of uncertain etiology	4	11
Pericarditis	1	2
No organic heart disease	4	13
Other significant medical conditions†		
Systemic hypertension	5	30
CVA and other thromboembolic phenomena	6	20
Diabetes mellitus	5	13
Chronic moderate to severe renal failure	2	9
Cancer	0	9
Presenting symptoms		
Syncope	10 (50%)*	13 (21%)
Dizziness, light headedness	4 (20%)	13 (21%)
Other symptoms not related to bradycardia	5 (25%)	20 (32%)
Asymptomatic	1 (5%)*	16 (26%)
Total	20	62

* Significant difference between groups ($p < 0.05$).
† Some patients had more than 1 condition.
CVA = cerebrovascular accident; SD = standard deviation.

Relationship to drugs: Prolonged pauses disappeared after discontinuing digoxin and propranolol in 2 patients, alpha methyldopa and propranolol in 1 patient, alpha methyldopa in 1, propranolol in 1, clonidine in 1, reserpine in 1 and amitriptyline and chlorpromazine in 1. In 6 patients pauses were caused by sinus node dysfunction and in 2 they were associated with bradytachycardia syndrome. Although pauses >2 seconds were not observed in these 8 patients after drugs were stopped, 2 patients with bradytachycardia syndrome and 1 with sinus node dysfunction continued to manifest electrocardiographic findings of sinoatrial disease. None of the patients with drug-induced prolonged pauses received a pacemaker. Two patients died, but in neither was the death related to the arrhythmia.

Associated conduction abnormalities: Twenty-three patients (27%) had associated atrioventricular (AV) or intraventricular conduction abnormalities or both. Nine patients had first-degree AV block, 5 second-degree AV block (4 Mobitz I and 1 Mobitz II) and 11 had right, 3 left and 3 unclassified bundle branch block. Five of these patients, including the patient with Mobitz II, received a pacemaker. Also, 24 patients with chronic atrial fibrillation and a slow ventricular response were considered to have concomitant AV nodal disease; 3 of these 24 also had an intraventricular conduction abnormality. Thus, in 44 patients (52%) with sinoatrial disease, there was electrocardiographic evidence of AV nodal or intraventricular conduction disease or both.

Symptoms: Presenting symptoms are listed in Table II. Seventeen of 82 patients (21%) had no symptoms and 25 (30%) had cardiac symptoms that could not be directly related to bradyarrhythmia. Thus, fewer than 50% of patients would have been expected to show symptomatic improvement after a pacemaker, yet 30% of pacemakers were implanted in such patients.

Relationship of pauses to symptoms: Pauses ranged from 2 to 15.2 seconds (average 2.6 ± 1.5, median 2.4). The mean of the longest pause was not a determinant of symptoms, survival or pacemaker insertion (Table III). Only 2 patients had an episode of transient loss of consciousness during the recording. Both patients had sinus bradycardia with a junctional escape rhythm and pauses ≤2 seconds. However, 16 of the 82 patients (20%) had pauses ≥3 seconds; only 2 of these patients had syncope. Six had no symptoms that could be related to their bradyarrhythmia. Four of these 16 patients received a pacemaker. Two of the 16 patients with markedly prolonged pauses died; 1 of them had received a pacemaker. Of the 3 patients with the longest pauses, none received a pacemaker, all are alive, and all are asymptomatic: The patient with a 15.2-second pause after a paroxysm of atrial flutter had no further episodes after clonidine was stopped; the patient with a 5.5-second interval of sinus arrest had no further pauses after amitriptyline and chlorpromazine were stopped; and the patient with a 4.4-second pause with atrial fibrillation continues to have pauses, but is asymptomatic.

Follow-up: Eighty patients were followed for an average of 12.8 ± 11 months (range 1 to 46); 17 (21%) died. The average survival of the 17 patients who died was 6.7 ± 7.2 months after the Holter study. Of these 17, 5 had received a pacemaker; the average survival of these 5 patients was 7 ± 4.6 months. There was no difference in the survival rate between patients who were paced and those who were not (Fig. 1). The average follow-up of patients who received a pacemaker was 14.7 ± 11 months; 25% of this group (5 of 20) died. The average follow-up of the patients who did not receive a pacemaker was 12.3 ± 11 months; 20% of this group (12 of 60) died. Thus, neither average follow-up nor likelihood of survival was different whether or not patients received a pacemaker.

The causes of death are listed in Table IV. In 1 patient the cause of death could not be determined. This patient had severe congestive heart failure with atrial fibrillation and recurrent, nonsustained ventricular tachycardia. She was admitted to another hospital before she died. Electrocardiograms at that time showed no bradyarrhythmias. Two patients died suddenly.

TABLE III Relationship of Pauses to Symptoms and Survival

	Mean ± SD	Range	Median
Patients receiving pacemakers	2.4 ± 0.5	2–3.8	2.3
Patients not receiving pacemakers	2.4 ± 0.3	2–15.2	2.4
Nonsurvivors	2.4 ± 0.4	2–3.2	2.4
All patients	2.6 ± 1.5	2–15.2	2.4
Symptoms			
Syncope	2.4 ± 0.5	2–4.2	2.2
Dizziness	2.6 ± 0.5	2–3.2	2.6
Asymptomatic or unrelated symptoms	2.8 ± 2.0	2–15.2	2.4

Values are in seconds.
SD = standard deviation

TABLE IV Causes of Death

	No. of pts.
CVA	3 (1)
Thromboembolism other than CVA	3 (1)
Renal failure	3 (1)
Metastatic cancer	2
Sudden death	2 (1)
Congestive heart failure and pneumonia	1 (1)
Aspiration pneumonia	1
Malignant hypertension	1
Unknown	1
Total	17 (5)

Parenthesis indicate number with pacemaker.
CVA = cerebrovascular accident.

They were elderly (86 and 94 years) and had unstable angina; 1 of them had received a pacemaker. No patient had a recognizable bradycardia-related death. In 6 patients, death was directly related to a thromboembolic episode and in 1 it was related to complications associated with a previous mesenteric artery thrombosis. All patients who had thromboembolism had the bradytachycardia syndrome or chronic atrial fibrillation.

Figure 2 shows the outcome of symptoms in both groups of patients. Symptoms, including syncope, generally improved whether or not the patient received a pacemaker. Five patients had recurrent syncope. In 4 patients a pacemaker was implanted. However, 1 patient who had 3 syncopal episodes before the diagnosis of the bradytachycardia syndrome did not receive a pacemaker and did not have a recurrence of this symptom.

Discussion

Since the natural history of patients with sinoatrial bradycardia is unknown, the decision to implant a permanent pacemaker in such patients is generally based on clinical intuition. Because of the widespread concern regarding the significance of the electrocardiographic findings associated with sinoatrial disease, pacemaker implantations for this abnormality have increased sharply and account in part for the recent upsurge in pacemaker implantations.[2] However, pacemakers have not been shown to prolong life in patients with sinoatrial disease. Moreover, the clinical significance of sinoatrial pauses discovered incidentally is unclear. In our study, which we believe to be the first to examine the association of the length of sinoatrial pauses to clinical manifestations, no relationship was found between the duration of sinoatrial pauses and the occurrence of symptoms, the severity of symptoms, the need for permanent pacemaker implantation or patient survival.

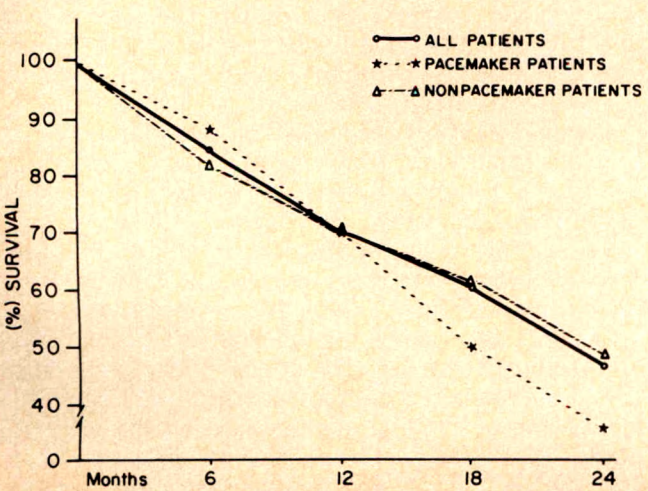

FIGURE 1. Survival rate of patients who received pacemakers compared with those who did not.

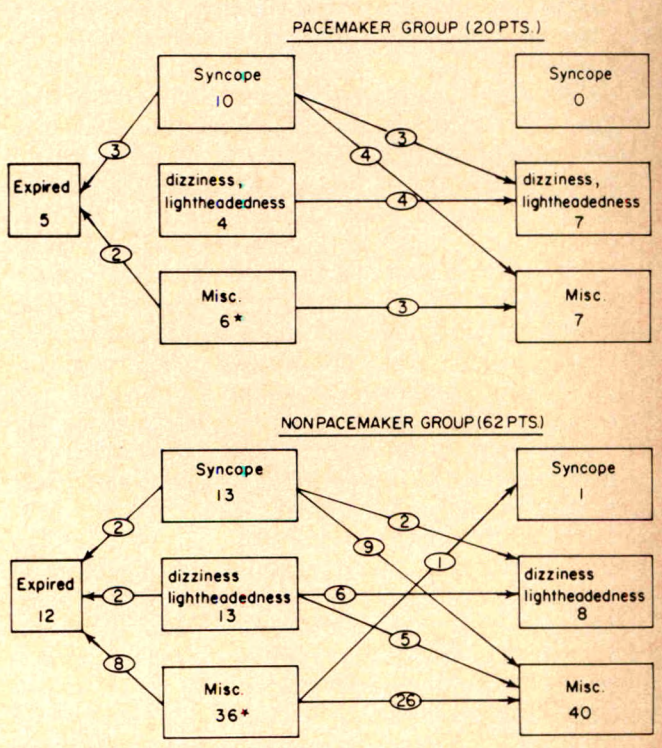

FIGURE 2. Initial symptoms and those at follow-up of patients who received pacemakers and those who did not.

While an abrupt cessation of cardiac output may result in a deficit in cerebral or coronary perfusion with its attendant effect producing either syncope or cardiac arrest, our study failed to identify a critical interval at which such events would be expected to ensue. Clearly, when such pauses produce serious symptoms, pacemaker implantation is indicated. Since the electrocardiographic manifestations of sinoatrial disease may be present for many years without adverse consequences,[10,11] the development of symptoms may be the result of systemic or regional hemodynamic changes rather than sudden, unpredictable occurrences of ventricular asystole. Whether a pause is likely to cause symptoms depends not only on the interval between heart beats, but also on the position and activities of the subject, regional vascular conditions and the capacity of the cardiac pump to generate sufficient pressure and to deliver an adequate stroke volume to maintain regional flow between cardiac cycles.

Prolonged sinoatrial pauses were observed in 2.6% of the patients in our study. Since these recordings were from patients at high risk for heart disease, this incidence might not reflect that found in otherwise healthy subjects. Brodsky et al[12] found sinoatrial pauses >1.75 seconds in 14 of 50 (28%) male medical students who had 24-hour Holter recordings. Viitaslo et al[13] found sinoatrial pauses >2 seconds on recordings from 13 of 35 (37%) endurance athletes and also in 2 of 35 (5.7%) matched nonathletic controls. Moreover, the electrocardiographic findings of sinoatrial disease may be present for many years in asymptomatic subjects.[13] Thus, presence of prolonged sinoatrial pauses per se cannot be considered to be an indication of cardiac malfunction.

To be viewed as beneficial, a pacemaker must improve survival or at least alleviate symptoms. Clearly, many patients with symptoms caused by sinoatrial disease obtain relief after pacemaker implantation.[5,14–17] However, pacemaker implantation has been suggested for asymptomatic subjects who have an arbitrarily selected slow heart rate or sinoatrial pause.[5,7] In our study, <50% of patients with prolonged sinoatrial pauses had symptoms that could be related to their bradyarrhythmia, yet 30% of pacemakers were implanted in such patients. Furthermore, implantation of pacemaker did not ensure that symptoms would improve. Seven of 20 patients (35%) who received a pacemaker continued to have central nervous system complaints after pacemaker implantation. This finding is in accord with an earlier report from our hospital that indicated that even after a critical policy of pacemaker implantation was instituted, 9% of patients who had a permanent pacemaker continued to have symptoms similar to those before implantation.[2] Previous reports have also shown that pacemakers do not always relieve symptoms in patients with sinoatrial disease.[6,18–21]

However, symptoms may spontaneously abate. In our study, 14 of 26 patients (54%) with symptoms ascribed to sinoatrial pauses who did not receive a pacemaker showed symptomatic improvement on follow-up. Similarly, Gann et al[5] found that 9 of 10 patients with syncope who did not receive a pacemaker had no further episodes during an average follow-up of 4.6 years. Rokseth and Hatle[6] observed that in 17 of 36 patients with syncope associated with sinoatrial disease, no treatment was considered necessary because either a single syncopal attack had occurred or slight symptoms persisted.

The electrocardiogram of sinoatrial disease may change over time.[5] Periods of electrocardiographic normalization[22] or a change to a stable chronic atrial fibrillation may eliminate the need for a permanent pacemaker in some patients.[23] The development of a stable chronic atrial fibrillation has been reported to occur in 11–37% of patients with sinoatrial disease.[16,19,23–25] Also, since both bradycardia and central nervous system symptoms are common in an elderly population, the failure of a pacemaker to produce symptomatic improvement may have been due to incorrectly attributing symptoms to the electrocardiographic abnormality.

Pacemaker implantation has not been shown to improve survival in patients with sinoatrial disease. Our study is consistent with previous reports.[4–6] Moreover, none of the deaths in our patients who did not receive a pacemaker could be ascribed to a bradycardic event. Previous studies, in fact, have not demonstrated a high risk of sudden death in patients with sinoatrial disease, and the occurrence of a bradycardia-related cardiac arrest appears to be rare in such patients. Our studies and previous natural history[11,14,22] and pacemaker follow-up studies[15–20,24,25] support the view that the survival of patients with sinoatrial disease is primarily determined by whether there is concomitant coronary disease, heart failure or systemic disease. The mortality rate in our patients appears to be a result of the high percentage of patients derived from a hospital population, in whom an increased incidence of severe systemic disease would be expected.

The limitation of our study and previous similar investigations is that they have been retrospective and nonrandomized. There may be an inherent bias in which patients who receive a pacemaker are likely to have more severe cardiac disease than those who do not. Such selection might obscure the possible beneficial effect of a pacemaker. In any case, although the issue is still unsettled, the evidence available fails to support the view that pacemakers improve survival in patients with prolonged sinoatrial pauses.

Clinical implications: Based on our experience and previous reports, the following approach to the management of prolonged sinoatrial pauses is suggested: Patients without symptoms do not require therapy. Nonessential bradycardia-producing drugs should be discontinued in symptomatic patients. Patients with bradytachycardia syndrome with prolonged pauses after episodes of tachycardia should receive a trial of antiarrhythmic therapy. Some patients may require such trials in a setting of continuous electrocardiographic monitoring or even with a temporary pacemaker in place. In symptomatic patients, especially when symptoms are vague and nonrepetitive, a clear relationship between the electrocardiographic abnormality and symptoms should be demonstrated. The role of

electrophysiologic studies in such patients is not clear because the studies have not been sufficiently reliable to predict which patients with sinoatrial disease require a pacemaker.[26] Perhaps such studies should be reserved for patients suspected of having occult tachyarrhythmias as an explanation for symptoms.

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Cardiac Arrhythmia and Conduction Disturbances During Sleep in 400 Patients With Sleep Apnea Syndrome

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This report presents the first study of cardiac arrhythmias and conduction disturbance in a large group (400 patients) with sleep apnea syndrome studied between 1974 and 1979 with 24-hour Holter electrocardiography and a simultaneously recorded polygraph during late afternoon or nocturnal sleep. Of the 400, 193 patients (48%) had cardiac arrhythmias during the recorded night. The mean number of apneic events, age, weight and lowest oxygen saturation during sleep were not significantly different in those with arrhythmias.

The most significant abnormalities were unsustained ventricular tachycardia in 8 patients, sinus arrest that lasted for 2.5 to 13 seconds in 43 patients, and second-degree atrioventricular conduction block in 31. Seventy-five had frequent (>2 beats/min) premature ventricular contractions during sleep. Fifty patients with significant arrhythmias had a tracheostomy and were monitored again after surgery. No arrhythmia was present in these patients except for premature ventricular contractions.

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In 1965 Gastaut et al[1] reported that some pickwickian patients had apnea during sleep.[1] In 1972, at the first international meeting on sleep apnea in Rimini, Italy, 3 teams presented hemodynamic studies on different kinds of patients with sleep apnea.[2–4] Each team showed that systemic blood pressure or pulmonary arterial pressure, or both, increased during sleep with sleep-related apnea. In 1977, we reported on cardiac arrhythmias occurring during sleep in 15 patients with sleep apnea syndrome. Fourteen of the 15 patients with obstructive sleep apnea syndrome had significant cardiac arrhythmias during sleep, although electrocardiograms (ECG) during wakefulness were normal.[5] Miller[6] also recently reported cardiac arrhythmias in 23 patients with sleep apnea. This is the first large study (400 patients) of the incidence and nature of cardiac arrhythmias during sleep in patients with sleep apnea syndrome.

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Methods

Patient group: The 400 patients surveyed included 16 women and 384 men with sleep apnea syndrome who met the following criteria: (1) they were seen at the Stanford Sleep Disorders Clinic between 1974 and 1979; (2) they had undergone simultaneous 24-hour Holter ECG and nocturnal polygraph recording; and (3) they were diagnosed as having sleep apnea syndrome (a score of >5 on the Apnea-Hypopnea Index).[7] During the same period, 187 patients seen in our clinic were rejected because they did not meet all the criteria. Retrospective investigation of these 187 patients showed that 111 of them had an apnea/hypopnea index of 5 to 40. The 400 analyzed subjects, who had an apnea/hypopnea index of 25 to 92, were, overall, more severely affected than the group excluded from the study. The women were 25 to 68 years old (median 59) and the men were 19 to 71 years (median 48). All subjects were referred for a sleep problem: 348 for daytime somnolence, 24 for disrupted nocturnal sleep, and 28 for heavy snoring at night and/or spousal observation of apneic events during sleep without significant sleep complaint. Of the 400, 354 (88.5%) had no other clinical syndrome associated with sleep apnea; 288 of these (72%) were 30 to 250% overweight. Forty-six nonobese subjects had sleep apnea syndrome associated with another condition: 12 acromegaly, 5 goiters, 1 Hodgkin's disease, 2 had received neck irradiation for other types of cancer, 3 Shy-Drager syndrome, 6 significant kyphoscoliosis (5 of these secondary to poliomyelitis), 8 myotonic dystrophy, 1 syringobulbomyelia, 6 micrognathia, and 2 Treacher-Collins' syndrome.

Cardiovascular disease and risk factors in the study group: Systemic hypertension had been diagnosed in 197 subjects (49%). In 20%, blood pressure was controlled by diet and nondrug treatment. During the previous 36 months, 117 subjects (29%) had taken antihypertensive medication. At the time of this study, 109 subjects had a blood pressure (supine) of ≥140 mm/Hg systolic and 90 mm/Hg diastolic. Sixty-nine subjects were receiving a diuretic medication (mostly chlorothiazide type) and 29 were taking propranolol hydrochloride. Late-onset, noninsulin–dependent diabetes had been diagnosed in 22 overweight subjects. Seven patients had had a myocardial infarction during the past 9 years; 8 were being treated for angina pectoris, and 12 had been hospitalized for unexplained chest pain. Four subjects had cardiac pacemakers implanted before consultation with the sleep clinic, 2 of whom had been referred immediately after pacemaker implantation because of their excessive daytime sleepiness. No patient was referred for a cardiovascular problem. Amphetamine had been prescribed for 161 subjects, and an additional 85 had had both amphetamine and methylphenidate prescribed for their daytime sleepiness. These two medications were discontinued at least 15 days before the investigation.

Fifty patients with severe sleep apnea syndrome underwent tracheostomy and were restudied 3 to 6 months after surgery with nocturnal polygraphic recordings and 24-hour Holter electrocardiogram.

Protocol: Each patient had a complete physical examination and a 12-lead ECG within 4 weeks of the first nocturnal investigation. At least 1 nocturnal polygraphic monitoring recorded the following variables: electroencephalogram (C3/A2—C4/A1 of the 10–20 international placement system), electrooculogram, digastric electromyogram and electrocardiogram (lead II). Respiration was monitored using oral and nasal thermistors and abdominal and thoracic mercury strain gauges or respiratory inductive plethysmography (Respitrace®). Arterial oxygen saturation was measured using a Hewlett-Packard ear oximeter (model 47201A).[8] The 24-hour Holter electrocardiographic recordings began between 12 and 4 PM on the day of nocturnal monitoring. The 24-hour ambulatory electrocardiographic recording was performed with an Avionics electrocardiographic tape recorder. All electrocardiographic tapes were processed by the Stanford computer-assisted method.[9,10] This technique enables accurate detection of all arrhythmias. The Holter electrocardiographic tracing and the polysomnogram were synchronized using the electrocardiographic lead on the sleep recording (Fig. 1). Polysomnograms were scored in 30-second epochs following Rechtschaffen and Kales' manual for scoring sleep states and

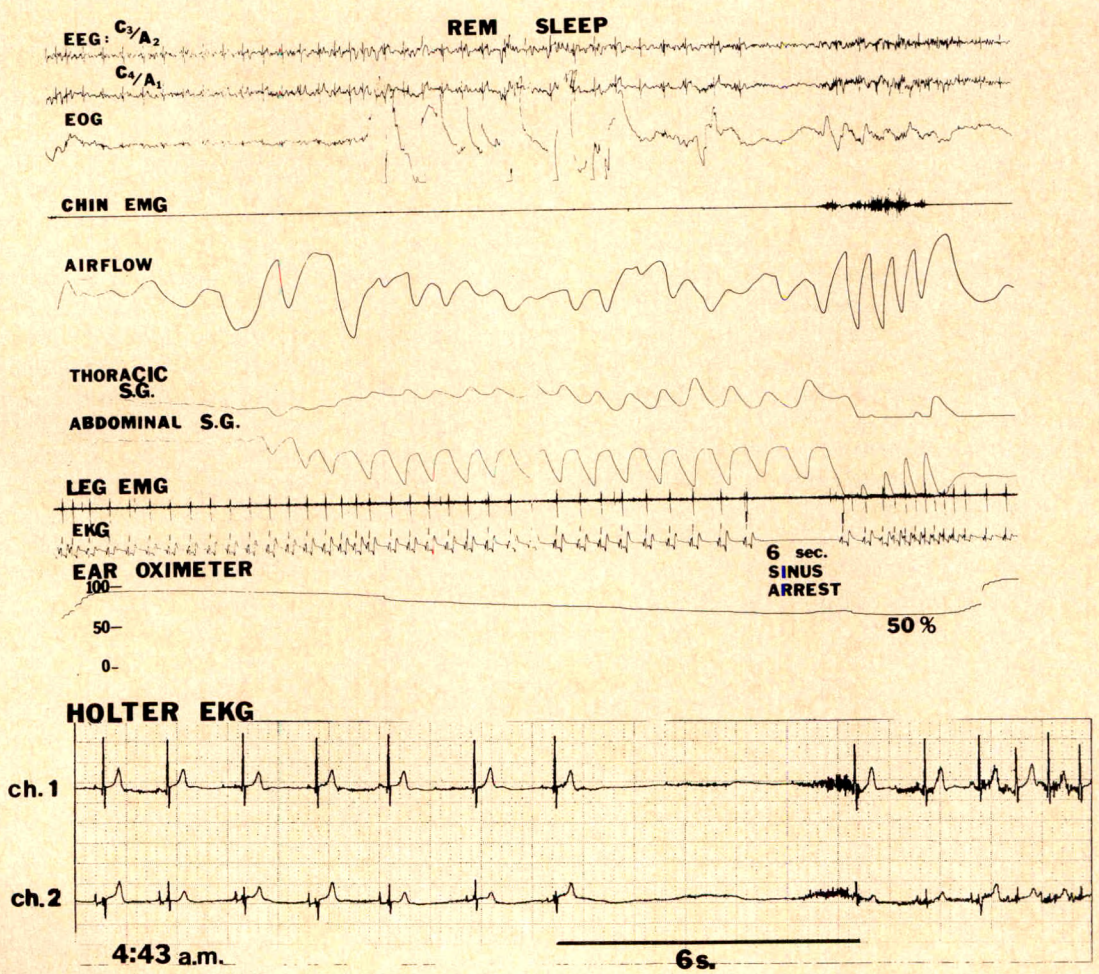

FIGURE 1. Segments of a polygraphic recording and Holter electrocardiogram (EKG) obtained from a 43-year-old man at 4:43 AM during REM sleep. Using the times written on both recordings, one can identify cardiac arrhythmias. With the polygraphic recording, one can correlate cardiac arrhythmias with sleep stages, sleep states, oxygen saturation and type of apnea. With the Holter electrocardiogram, one can accurately detect all arrhythmias and play back the tape for analysis at conventional speed. EEG = electroencephalogram; EMG = electromyogram; EOG = electrooculogram; SG = strain gauge.

TABLE I Cardiac Arrhythmias and Conduction Abnormalities Seen During Sleep in Association With Sleep Apnea Syndrome

Arrhythmia or Conduction Abnormality	Percent of Total Population	Patients (n)
Sinus arrest (2.5 to 13 s)	11	43
Second-degree atrioventricular cardiac block		
Mobitz type I	5	19
Mobitz type II	3	12
Ventricular tachycardia	3	12
Atrial tachycardia	7	28
Sinus bradycardia (<30 beats/min for at least 10 s)	7	29
Paroxysmal atrial fibrillation	3	10
Paroxysmal atrial flutter	1	3
Frequent premature ventricular contractions (>2/min)	20	75*

* Only 40 patients had premature ventricular contractions not associated with other arrhythmia during sleep.

TABLE II Cardiac Arrhythmia or Conduction Abnormality in 50 Patients With Sleep Apnea Syndrome Before and After Tracheostomy

Cardiac Arrhythmia or Conduction Abnormality	Before Tracheostomy		After Tracheostomy	
	Awake	Asleep	Awake	Asleep
Sinus arrest 4 to 13 s	0	15	0	0
Second-degree atrioventricular block				
Mobitz type I	0	5	0	0
Mobitz type II	0	10	0	0
Ventricular tachycardia	0	8	0	0
Atrial flutter	0	2	0	0
Atrial fibrillation	0	8	0	0
Extreme sinus bradycardia	0	2	0	0
Frequent premature ventricular contractions (>2/min)	6	18*	4	4

* A number of patients had several types of cardiac arrhythmia: 4 with runs of ventricular tachycardia also had frequent premature ventricular contractions (>2/min); 8 patients with second-degree block; 2 with atrial fibrillation; and 2 with sinus arrest also had premature ventricular contractions. Two patients had sinus arrest in association with extreme sinus bradycardia (heart rate <30 beats/min). Only 2 patients presented frequent premature ventricular contractions independent of other arrhythmias.

stages.[11] Apneic and hypopneic episodes were identified and scored using the criteria of Guilleminault et al[7] (defined as the number of abnormal respiratory events divided by total sleep time and multiplied by 60). Hypopnea was defined as a decrease of air exchange at the nose and mouth with increased thoracoabdominal movements (incomplete airway obstruction) or decrease of thoracoabdominal movement with decrease of airflow, in both cases accompanied by a simultaneous decrease in oxygen saturation.[7]

Results

Cardiac arrhythmias or conduction disturbances were present during sleep in association with sleep apnea in 193 patients (48%). The mean age of affected patients was 49 years; all but 1 were male, and 84% were obese. They had a mean apnea-hypopnea index of 42 (range 25 to 88). The lowest oxygen saturation during sleep in individual patients ranged from 30 to 64% (H-P ear oximeter values).[8] There were no important differences in age, body weight, apnea-hypopnea index or minimum oxygen saturation between those with and those without arrhythmias (Wilcoxon matched pair rank test). The incidence of hypertension and of diuretic or beta-blocking drug intake was similar in both groups.

Among the other 207 patients (without cardiac arrhythmias during the monitoring night), the lowest apnea-hypopnea index was 20 and the highest 92. The mean apnea-hypopnea index was 42.8. The lowest oxygen saturation measured during sleep varied between 62% and <30%.[8] Fewer patients in the arrhythmia group had angina pectoris or had had a myocardial infarction (2 versus 13). The small subgroup of patients (10%) with predominantly central sleep apnea were different from those with obstructive apnea in that only 1 had any arrhythmia other than premature ventricular contractions (PVCs) (a 6-second sinus node arrest). Except for PVCs, cardiac arrhythmias were only seen when the oxygen saturation was <72%, and 93% of these were observed with an ear oximeter reading ≤65%. These arrhythmias always occurred during the second half of an apneic event, and 98% occurred during an obstructive event or during the obstructive phase of a mixed apneic event.

Eight patients had a single episode of unsustained ventricular tachycardia 5 to 11 beats in duration (Table I). Sinus node arrest (2.5 to 13 seconds) occurred in 43

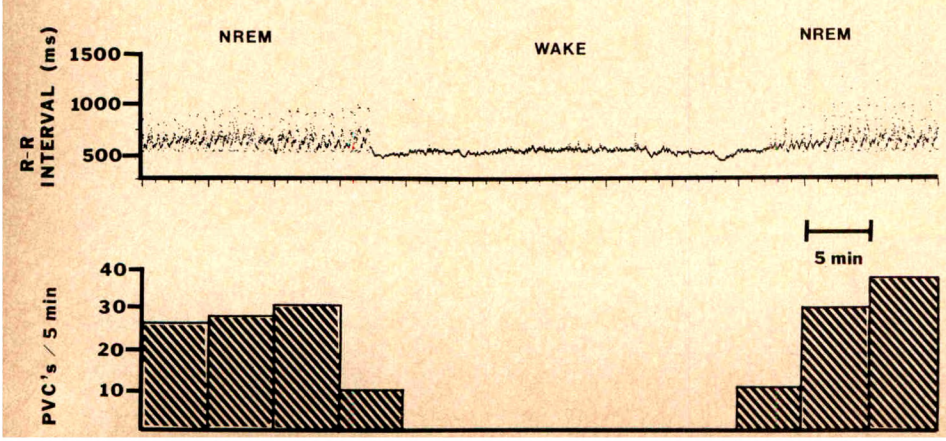

FIGURE 2. The relation between the frequency of premature ventricular contraction (PVCs) and sleep. Each **dot** in the **upper panel** shows 1 R-R interval. The **lower panel** shows the frequency of premature contractions. Note the cyclic pattern of R-R intervals during non-REM (NREM) sleep associated with sleep apnea. PVCs decrease greatly on waking.

patients; in 32 patients it was ≥4 seconds in duration. Second-degree atrioventricular nodal conduction block occurred in 31 patients; 19 had Mobitz type I and 12 had Mobitz type II. All episodes of ventricular tachycardia, sinus arrest, and second-degree atrioventricular block occurred only during obstructive sleep apnea in stage 2 sleep or in REM sleep. Frequent PVCs (2/min) during sleep occurred in 75 patients (20%), 35 of whom also had other arrhythmias during sleep. In 55 patients, PVCs were clearly sleep-related and their frequency decreased when the patients awoke, even for short periods of time (Fig. 2). In the subgroup of patients with a previously known cardiac problem (myocardial infarction or angina) and sleep apnea, 2 patients had more frequent PVCs during wakefulness than during sleep. Except for PVCs, no patient with significant cardiac arrhythmia during sleep had any arrhythmia during wakefulness. Sinus arrest was seen in 3 patients who had extreme sinus bradycardia at other times during the night. Extreme sinus bradycardia occurred concurrently with obstructive sleep apnea during nonREM sleep in these 3 patients, whereas sinus arrest was noted during REM sleep. The REM sleep apneic events leading to asystoles were no longer than those leading to extreme sinus bradycardia.

Cardiac arrhythmia and tracheostomy: Fifty patients with arrhythmias during sleep apnea underwent tracheostomy, 37 of whom have been reported previously.[12] The number of cardiac arrhythmias and conduction abnormalities occurring during sleep and while awake both before and after tracheostomy are presented in Table II. Three to 6 months after successful tracheostomy, no arrhythmia or conduction abnormality was detected in 46 patients during sleep on electrocardiographic Holter recordings. Frequent PVCs were still present in 4 patients during the 24-hour period, but decreased during sleep in all 4.

Discussion

This study demonstrates that cardiac arrhythmias and conduction abnormalities commonly occur during sleep in patients with sleep apnea syndrome. To assess the importance of rhythm disturbances that were found in the patients in this study, it is helpful to compare the frequency with which arrhythmias are recorded by 24-hour Holter electrocardiography in large groups of healthy subjects without diagnosed sleep apnea. Several studies have shown that sinus arrest lasting longer than 2.5 seconds and sinus bradycardia of <30 beats/min do not occur in asymptomatic, healthy subjects,[13–17] although 0.7 to 6% of asymptomatic subjects have some episodes of second-degree atrioventricular nodal block, predominantly Mobitz type I. The sinus arrest and extreme bradycardias that occur in some patients with sleep apnea is abnormal and is a potentially life-threatening complication of sleep apnea syndrome.

Frequent PVCs and episodes of nonsustained ventricular tachycardia are both reported to occur in asymptomatic subjects studied by Holter electrocardiography. Frequent PVCs are seen in 0 to 12% and ventricular tachycardia in 0 to 4% of subjects; the frequency of both arrhythmias appears to increase with age,[13–17] even in patients who have been screened for heart disease. Both PVCs and ventricular tachycardia were more frequent during periods of wakefulness than during sleep in these population surveys, and when they did occur nocturnally, sleep apnea syndrome (a condition frequently overlooked) was not specifically excluded. Frequent PVCs were detected in 20% of our patients, a higher incidence than that reported for asymptomatic populations. However, we had more cases of obesity and hypertension in our patients. Both our patients and the reported asymptomatic subjects had a similar incidence of ventricular tachycardia (4%). In our study, however, all 8 episodes of ventricular tachycardia occurred during a sleep apneic event. This is in marked contrast to the general daytime occurrence of frequent PVCs and episodes of ventricular tachycardia in studies of asymptomatic subjects.[13–16] More than half of our subjects with frequent PVCs and bigeminy and trigeminy had predominantly nocturnal PVCs, suggesting a relation between arrhythmias and sleep apnea. Our study raises the possibility that the occurrence of arrhythmias in asymptomatic population groups may in some cases be related to sleep apnea syndromes. Without systematic interviews to evaluate sleep behavior, patients with sleep apnea may be included in surveys of "normal" populations.

Fifty patients in this study underwent tracheostomy. After surgery, no patient had arrhythmias other than PVCs, further supporting the contention that the sleep apnea episodes caused the arrhythmias.

The sinus and atrioventricular nodes are strongly influenced by autonomic tone; atrial and ventricular arrhythmias are affected by neurologic, psychologic and autonomic factors.[18] The autonomic activity present during sleep may affect the heart.[19] During sleep apnea episodes, there is evidence of heightened autonomic activity.[20] The mechanism by which sleep apnea causes arrhythmias is not known, but autonomic nervous system imbalance and arterial oxygen desaturation are likely to be important factors. In some patients, underlying cardiac disease may also contribute to the arrhythmias.

In summary, we found cardiac arrhythmias (some potentially life-threatening) to be common in patients with sleep apnea syndrome. These almost always occurred in association with an episode of obstructive apnea. Tracheostomy eliminates both the sleep apnea and the arrhythmias.

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Encainide for Refractory Ventricular Tachyarrhythmia

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Encainide, a new antiarrhythmic agent, was studied in 80 patients with sustained ventricular tachycardia or ventricular fibrillation. Drug efficacy was evaluated by ambulatory monitoring and exercise testing in 63 patients who had frequent or repetitive ventricular premature beats and by means of electrophysiologic testing in 17 patients who did not have significant arrhythmia during a 48-hour control period. Encainide was effective in 36 of 63 patients (57%) as judged by ambulatory monitoring and in 35 of 51 patients (69%) who had exercise tests while taking the drug. Overall, 34 patients (54%) responded to encainide when evaluated by both monitoring and exercise testing. The drug was effective in 7 of 16 patients (44%) who underwent electrophysiologic studies. Daily doses and blood levels of encainide were comparable in responders and nonresponders. Toxicity occurred in 24 patients (30%) and included nausea, vomiting, headaches, lethargy, tremors and conduction disturbances. In 18 patients (23%) arrhythmia was aggravated. An increase in arrhythmia correlated with larger daily doses of encainide and higher serum blood levels of encainide and its metabolite OD-methyl-encainide, but did not correlate with QRS- or QT-interval widening. Of the 27 patients who were discharged on encainide, 23 were maintained on the drug for an average of 21 months (range 12 to 44). Three patients died suddenly.

Thus, encainide is a useful agent for suppression of malignant ventricular arrhythmias. However, it has a high potential for worsening arrhythmias and careful evaluation by both monitoring and exercise testing is necessary to judge its effect.

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An increasing number of patients with life-threatening ventricular arrhythmias are being identified and are in need of treatment. This has stimulated the introduction of a number of antiarrhythmic drugs that are undergoing active investigation. One such agent is encainide, a newly developed benzanilide derivative with promising antiarrhythmic properties in short-term animal studies.[1,2] In isolated canine cardiac Purkinje fibers, encainide exhibits potent local anesthetic properties or membrane-stabilizing effects.[3] At concentrations of $>10^{-5}$ mol, encainide exerts significant depressant action, resulting in reduced action potential amplitude and upstroke velocity (dV/dt max). Action potential duration is shortened, the refractory period is unaffected and automaticity is decreased. Several studies involving a small number of patients have reported that encainide was effective in suppressing ventricular arrhythmias unresponsive to standard antiarrhythmic drugs.[4–7] This report presents results of encainide in a large group of patients with diverse forms of heart disease who experienced frequent, symptomatic ventricular arrhythmia refractory to conventional drugs.

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Methods

Patients: The group consisted of 80 patients, 59 men and 21 women, with an average age of 54 years (range 19 to 76) (Table I). All patients had documented malignant, sustained and recurrent ventricular arrhythmias. The term malignant defines a group with life-threatening arrhythmias consisting of either ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) manifested by serious hemodynamic compromise and requiring countershock or antiarrhythmic drugs for termination. Patients whose VT was either transient or unaccompanied by symptoms were not included in this study. In the present group persistent VT resulted in syncope in 28 patients or hypotension and dizziness in 31. Twenty-one of the 80 patients experienced VF from which they have been successfully resuscitated. These patients had been referred for medical management because of their refractoriness to conventional agents including procainamide, quinidine, disopyramide and propranolol. The arrhythmia was considered to be refractory to a drug if a sustained episode recurred at a

TABLE I Data in 80 Patients (59 Men and 21 Women, Average Age 54 Years (Range 19 to 76)

Cardiac disease	
Coronary artery	45
Previous myocardial infarction	42
Cardiomyopathy	11
Valvular	8
None demonstrable	16
Presenting arrhythmia	
Ventricular tachycardia	59
Ventricular fibrillation	21
Congestive heart failure	45

time when the drug level was within the therapeutic range. Cardiac diagnoses included coronary artery disease in 45 patients, 42 of whom had a history of a remote myocardial infarction; cardiomyopathy in 11; and valvular heart disease in 8. In 16 patients no heart disease was seen on cardiac catheterization or echocardiography. Forty-five patients (56%) had a history of congestive heart failure and exhibited cardiomegaly on the chest roentgenogram. At the time of study all were hemodynamically compensated and were receiving maintenance digoxin or diuretic therapy.

Protocol: *Control studies:* On admission to the hospital all cardioactive drugs were discontinued. Digoxin was maintained when congestive heart failure had been historically documented. After 36 to 48 hours off the drug, control studies were performed. These consisted of 48 hours of continuous ambulatory electrocardiographic monitoring and maximal exercise testing on a motorized treadmill adhering to a Bruce protocol.[8] The details of this control phase of the study have been described.[9,10]

Ventricular premature beats (VPBs) were categorized according to the Lown grading system[9,11]: grade 0: no VPBs; grade 1A: ≤30 VPBs, ≤1/min; grade 1B: ≤30 VPBs, >1/min; grade 2: >30 VPBs; grade 3: multiform VPBs; grade 4A: repetitive VPBs (couplets); grade 4B: repetitive VPBs (ventricular tachycardia); and grade 5: early (R on T) VPBs.

Evaluation of therapy: The protocol to be followed was determined by the frequency and type of ventricular arrhythmia present during control studies.[10] Noninvasive antiarrhythmic drug evaluation was performed if the following arrhythmias were exposed: during monitoring, grade 2 VPBs during at least 50% of monitored hours, and grade 4 VPBs for at least 3 of the 24 hours; during exercise testing, at least 2 VPBs/min during the entire exercise test, and grade 4 VPBs during exercise or recovery periods.

If these criteria were not met, the patient underwent electrophysiologic studies.[12] Under fluoroscopic guidance, a No. 6Fr hexapolar pacing catheter was inserted percutaneously into the left subclavian vein and positioned at the right ventricular apex. The catheter was sutured to the chest wall so that its position was stable. Programmed premature stimulation was performed using ≤3 successive extrastimuli at energies of 2 and 3 times the mid-diastolic threshold. Studies were carried out during both sinus rhythm and ventricular pacing at a cycle length of 500 ms. The end point for the electrophysiologic study was the provocation of nonsustained VT, defined as ≥3 successive ventricular beats occurring after the last premature beat provoked by programmed stimulation. In all cases this end point was reproducible, being induced at least twice at the same coupling cycle.

Protocol for drug administration: At the conclusion of baseline studies, oral encainide therapy was initiated, adhering to the following schedule: On day 1 an acute drug test[9,10] with oral encainide was carried out. During a 30-minute control period the electrocardiogram was continuously recorded by trendscription[13] and exercise was performed on a bicycle ergometer for 5 minutes. At the conclusion of this control period 75 mg of encainide was administered as a single oral dose. The electrocardiogram was continuously monitored and recorded for 3 hours. Each hour a 5-minute bicycle exercise was repeated and a lead II and V_3 rhythm strip recorded at 50 mm/s for a measurement of electrocardiographic intervals. Eight hours after this dose, 25 mg of encainide was administered. On day 2, the dosage was 20 or 25 mg 4 times daily; on day 3, 20 or 25 mg alternating with 50 mg 4 times daily; on day 4, 50 mg 4 times daily; on day 5, 50 mg alternating with 75 mg 4 times daily; and on day 6, 75 mg 4 times daily.* Patients were observed in a special care unit and were seen daily by the medical staff as well as by one of the investigators and a research nurse-clinician. During encainide administration, patients were continuously monitored by telemetry and the rhythm was recorded by means of trendscription. Each day before a change in the dose of encainide patients performed on a bicycle ergometer for 5 minutes, and leads II and V_3 rhythm strips at 50 mm/s were obtained for electrocardiographic intervals. At least 3 complexes were measured. Patients were questioned carefully to ascertain the occurrence of adverse effects. A decision to increase the dose of encainide depended on the absence of adverse effects and the persistence of arrhythmia on trendscription or during bicycle exerise. If adverse effects developed, the dose was decreased to that tolerated. The response to therapy was evaluated after at least 48 hours of treatment with a stable dose. Blood levels for encainide and OD-methyl-encainide levels were determined 2 hours after drug administration.

The response to encainide was evaluated either with noninvasive techniques that included both exercise testing and ambulatory monitoring or with invasive electrophysiologic testing.

On the basis of our experience with management of patients with malignant ventricular arrhythmia,[14] encainide was deemed effective if the following 3 criteria were fulfilled for noninvasive evaluation with both monitoring and exercise testing: total elimination of grade 4B and 5 VPBs; ≥90% reduction in the frequency of grade 4A arrhythmia (couplets); and ≥50% decrease in the number of hours during which grade 2 arrhythmia occurred with monitoring and >50% reduction during exercise testing.

The criterion for drug efficacy with electrophysiologic testing was the inability to provoke multiple repetitive ventricular responses (>2) during either sinus rhythm or ventricular pacing using up to 3 successive premature stimuli at 3 times mid-diastolic threshold.[12] Encainide was considered effective if only a single repetitive response was elicited. The cycle length used was the same as during control study.

Long-term therapy: Initiation of chronic therapy with encainide depended on 3 factors: fulfillment of criteria for efficacy, absence of significant adverse effects, and encainide considered the most effective and best tolerated of all the drugs tested. Patients were followed up every 1 to 2 months with repeat monitoring, exercise testing, and blood sampling for chemistries as well as for encainide and the metabolite OD-methyl-encainide.

Statistical analysis was performed with the *t* test for paired data and the chi-square test. All results were expressed as mean ± standard deviation and the level of significance was $p < 0.05$.

*After the first 10 patients in the study, 50 mg 4 times daily was established as the maximal dose by the sponsoring pharmaceutical company, Mead Johnson.

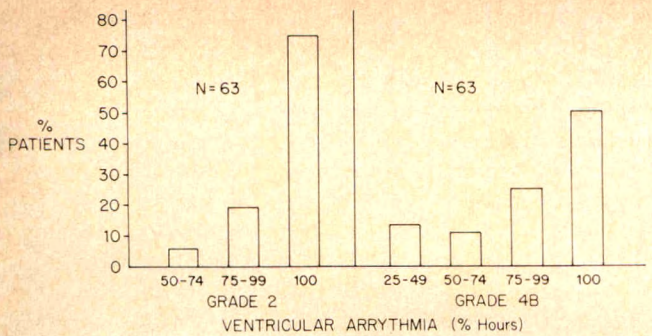

FIGURE 1. Frequency of grades 2 and 4 ventricular arrhythmia during control studies among the 63 patients who underwent noninvasive evaluation of encainide. All patients had frequent ventricular premature beats (grade 2) for >50% of the monitored hours, whereas 48 patients (75%) had grade 2 for all hours (**left**). All patients had ventricular tachycardia (grade 4B) for >25% of the hours monitored (**right**), and in 32 patients (50%) these forms were present during each hour.

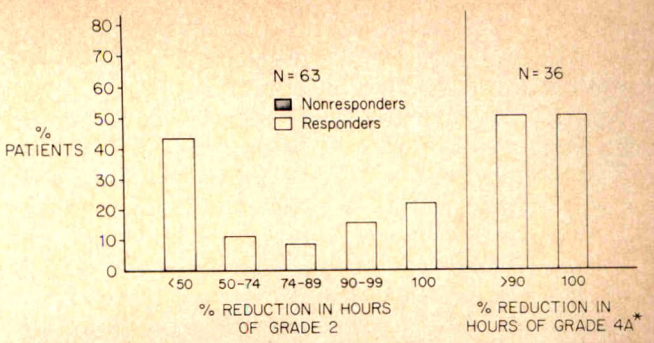

FIGURE 2. Results of encainide therapy as evaluated by 24-hour ambulatory monitoring. Encainide was ineffective in 43% of patients (**left**). In the 36 responders (57%), the hours of frequent ventricular premature beats (grade 2) was decreased by >75% in 24 patients, whereas grade 2 arrhythmia was abolished during all hours in 14. Grade 4 arrhythmia was entirely abolished in 18 patients, whereas all grade 4B was eliminated and grade 4A reduced >90% in 18. *All patients had total elimination of 4B.

Results

Control studies: Of the 80 patients treated with encainide, 63 had noninvasive evaluation for drug efficacy with exercise testing and monitoring and 17 underwent invasive electrophysiologic studies.

In all 63 patients who had noninvasive studies, control monitoring demonstrated frequent salvos of VT, and in 54 (86%) such paroxysms were present during >50% of the hours monitored (Fig. 1). In 59 patients (94%) frequent VPBs (grade 2) were present during >75% of the hours.

Of the 51 patients who underwent exercise testing, all exhibited frequent VPBs (mean frequency 230, range 100 to 540) and couplets (mean 21 per test). In 35 of these patients salvos of VT were provoked as well. The remaining 12 patients did not undergo exercise testing because of frequent salvos of VT with hemodynamic instability that occurred in the coronary care unit after antiarrhythmic drugs were discontinued.

Of the 17 patients who underwent electrophysiologic testing during control study, 5 had nonsustained VT (average 8 cycles, range 6 to 12). Eleven patients responded with sustained VT (average rate 193, range 160 to 280) and 1 patient had VF. One additional patient required cardioversion because of hemodynamic instability, and in 10 overdrive pacing terminated the VT.

Drug efficacy with noninvasive evaluation: Encainide was effective in 36 of 63 patients (57%) when evaluated by ambulatory monitoring. In 18 of these patients grade 4 or repetitive VPBs were entirely abolished and in the other 18 grade 4B was eliminated, grade 4A was reduced by ≥90% and the number of hours of grade 2 was reduced by ≥50%. Twenty-four patients had ≥90% decrease in VPB frequency (Fig. 2). In 27 patients encainide was judged ineffective. Although paroxysms of VT persisted, the rate of the arrhythmia was significantly decreased from a mean of 202 to 142 beats/min; however, the mean length of each salvo was unaltered.

Thirty-five of the 51 patients (69%) who had repeat exercise testing responded to encainide. VPBs were reduced from a control of 225 per test to 26 during encainide therapy. In 31 of the responders, couplets as well

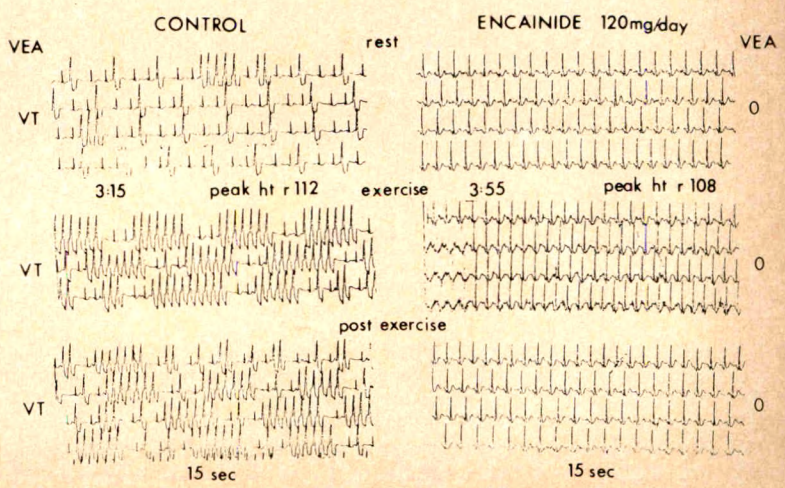

FIGURE 3. Electrocardiographic tracings from a patient who responded to encainide. During control studies frequent salvos of ventricular tachycardia (VT) were present during all hours of monitoring. Exercise testing increased the frequency of VT as well as length of the salvo. After 4 days of encainide therapy, ventricular arrhythmia was entirely abolished. VEA = ventricular ectopic activity.

as 4B arrhythmia were abolished. In the 35 responders the mean frequency of couplets was 21 per test in the control study and 0.3 during encainide therapy.

Overall, 34 patients (54%) responded to encainide when evaluated by both monitoring and exercise testing (Fig. 3). The mean dose in the responders was 152 ± 64 mg/day and that in nonresponders was 129 ± 46 mg/day. This difference was not statistically significant. The serum blood level of encainide in responders and nonresponders was 116 and 119 ng/ml, respectively, whereas values of OD-methyl-encainide were 98 and 100 ng/ml, respectively. These concentrations were not significantly different. Widening of the QRS complex was observed in 9 patients, but this did not correlate with response or drug level. There was no correlation between the underlying heart disease, presenting arrhythmia and efficacy of encainide.

Electrophysiologic studies: One patient who underwent electrophysiologic testing with encainide developed severe adverse effects (nausea and vomiting) that necessitated discontinuation of the drug before evaluation. Of the remaining 16 patients, 7 (44%) responded to encainide (Fig. 4). Six patients had sustained VT that had been provoked during control studies, whereas 1 patient had nonsustained VT. In 9 patients the drug failed to prevent the provocation of arrhythmia, although the rate of the VT with encainide therapy was slowed (202 versus 170 beats/min). The mean dose of the drug in responders and nonresponders was comparable (167 versus 179 mg/day). Overall, 41 of the 79 patients (52%) responded to encainide when evaluated with noninvasive or invasive studies.

Adverse effects: Toxicity occurred in 24 patients (30%) (Table II). This included severe nausea and vomiting, headaches, profound lethargy and tremors. One patient with pronounced QRS widening before receiving the drug developed third-degree atrioventricular block. In 18 patients (23%), arrhythmia was aggravated (Table II). The arrhythmia was aggravated in patients with and without heart disease. This occurred in 5 of the 10 patients who received >200 mg/day and in 13 of the remaining 70 patients (18.6%) receiving smaller doses of encainide. In 2 patients VF occurred for the first time; 1 patient had nonsustained VF (Fig. 5). Three patients who were free of advanced grades of ventricular ectopic activity and in whom VT occurred only with electrophysiologic testing had spontaneous salvos of VT at rest while taking encainide. Three patients who had nonsustained VT during control electrophysiologic testing had sustained VT with syncope provoked while receiving encainide. Cardioversion was required in each case. In these patients, VT was more easily provoked; that is, fewer extrastimuli were used compared with control testing. The remaining 9 patients who underwent noninvasive studies had sustained VT with encainide, although in control studies only short paroxysms of sustained VT occurred. In 7 of these patients, ambulatory monitoring while taking encainide showed a reduction of arrhythmia, but exercise provoked sustained VT that had not occurred with exercise. Cardioversion or another antiarrhythmic drug (lidocaine or procainamide administered intravenously) were required in each. The dose of drug and the blood levels were significantly higher for those exhibiting aggravation (that is, 191 and 178 ng/ml, respectively). The level of the OD-methyl-encainide metabolite was also higher than in patients in whom encainide was effective (307 ng/ml) ($p < 0.005$). Widening of the complex QRS did not predict aggravation of arrhythmia and occurred in only 5 of the 18 patients.

Long-term therapy: Twenty-seven patients were discharged on encainide. The type of heart disease in these patients was similar to that in the whole group. The basis for its selection included efficacy, absence of adverse effects and patient preference (Table III). Twenty-three patients continued therapy for an average of 21 months (range 12 to 44). Persistent and increasing lethargy compelled discontinuation of encainide in 1 patient. Four patients died: 1 from progressive congestive heart failure after 13 months of therapy, and in 3 death was sudden. These 3 patients had a history of VT with syncope.

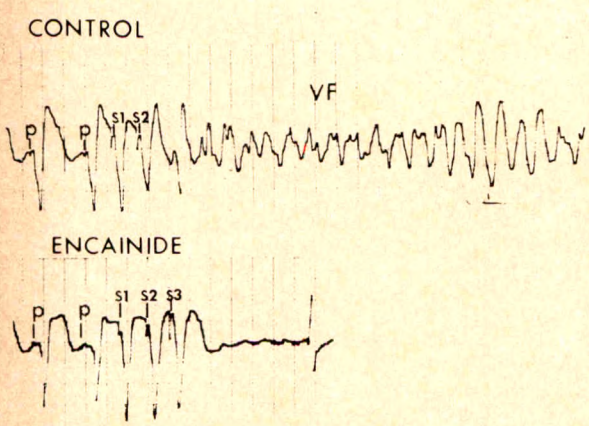

FIGURE 4. Electrocardiographic tracings from a patient who responded to encainide during invasive electrophysiologic testing. During control studies, 2 extrastimuli (S_1 and S_2) added during ventricular pacing (p) provoked ventricular fibrillation (VF). When the patient received encainide, as many as 3 extrastimuli (S_1, S_2 and S_3) failed to provoke repetitive responses.

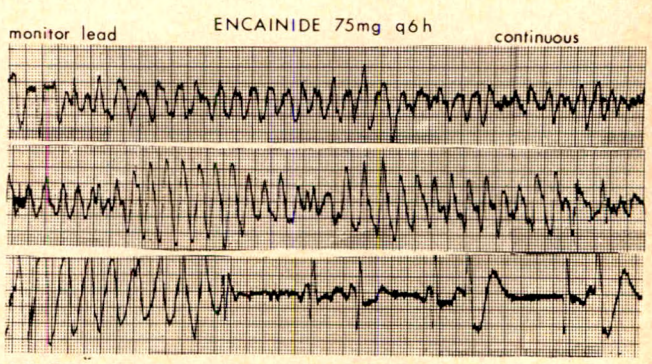

FIGURE 5. Aggravation of arrhythmia in a 30-year-old woman who had mitral valve prolapse and frequent ventricular premature beats with short salvos of uniformed ventricular tachycardia that were provoked during exercise testing. After 4 days of encainide therapy she complained of dizziness and had 4 syncopal episodes. Monitoring during this time demonstrated nonsustained ventricular fibrillation.

TABLE II Adverse Effects Observed in 24 of 80 Patients Treated With Encainide

Atrioventricular block	1		
Tremor	1		
Headache	2		
Lethargy	1		
Nausea	1		
Aggravation of arrhythmia	18		
First occurrence of ventricular fibrillation		3	
Salvos of ventricular tachycardia converted to sustained episodes		12	
Electrophysiologic testing			3
Noninvasive evaluation			9
Spontaneous salvos of ventricular tachycardia at rest		3	

TABLE III Long-Term Results in 27 Patients Treated With Encainide

Coronary artery disease	20	
Cardiomyopathy	4	
Valvular	1	
None	2	
Discontinued drug	5	
Adverse effect		1
Death		4
Arrhythmia		3
CHF		1

Average Follow-Up Dose (mg/day)	21 Months (12–44) (n = 22)
80	5
100	2
120	5
150	3
200	6
300	1

CHF = congestive heart failure.

Discussion

Protecting the patient against a recurrence of malignant ventricular arrhythmia requires individualized therapy with antiarrhythmic drugs.[9] In the Seattle Heart Watch program, the recurrence rate of ventricular fibrillation was 26% during the first year of follow-up regardless of the antiarrhythmic therapy administered to two thirds of these patients.[15] However, therapy was empiric, without systematic drug evaluation. An effective medical program mandates ascertainment of drug efficacy.

Establishment of an effective treatment program requires the adherence to precise standards for assessing drug efficacy. Our criteria include complete abolition of grade 4B and 5 VPBs, ≥90% reduction in couplets, and ≥50% reduction in frequency of VPBs during both ambulatory monitoring and exercise stress testing. During electrophysiologic studies drug efficacy is defined as the inability to provoke multiple repetitive responses during both sinus rhythm and ventricular pacing. When patients are managed with antiarrhythmic drugs using these criteria, survival is improved.[12,14] This was demonstrated in 123 consecutive patients who frequently experienced recurring life-threatening ventricular arrhythmias.[14] Among 98 patients in whom the criteria for drug effectiveness were met, the annual incidence of sudden death was only 2.3%, compared with the 50% annual mortality rate in the 25 patients in whom control was not achieved. There were no clinical variables, including extent of left ventricular functional impairment, that distinguished the 2 groups.

Our success rate with encainide was 52%—less than that of Roden et al,[4] who reported nearly complete abolition of ventricular arrhythmia in 10 of 11 patients. Their patients had frequent VPBs, but had not experienced sustained life-threatening ventricular tachyarrhythmias. Furthermore, Roden et al excluded patients with angina pectoris or those who had congestive heart failure. Mason and Peters[5] reported a response rate similar to ours, with a 54% effectiveness among 35 patients treated with encainide for symptomatic VT. However, different criteria of efficacy were used. Mason and Peters adjudged the drug effective when symptomatic arrhythmia was prevented even if salvos of VT persisted. In contrast, we stipulated complete elimination of grade 4B or 5 VPBs during both ambulatory monitoring and maximal exercise stress testing.

Adverse effects: Antiarrhythmic drugs may worsen ventricular arrhythmias. Velebit et al[16] studied a large number of antiarrhythmic agents and found recorded aggravation of arrhythmia in 6 to 16% of drug studies. Mason and Peters[5] reported worsening of arrhythmia in 4 of 36 patients (11%) receiving encainide. In 1 patient the frequency of salvos of VT increased and in 3 VF occurred for the first time. Nicholson et al[7] observed an increase in arrhythmia during electrophysiologic study in 4 of 17 patients (23%). DiBianco et al[17] described the occurrence of sustained VT in 3 of 20 patients (15%) treated with encainide for chronic ventricular premature beats.

In our study 23% of patients treated with encainide had worsening of arrhythmia. However, this adverse effect was related to drug dosage. Thus, the incidence was 50% in patients who received >200 mg/day and 18.6% for those who received a smaller dose. That the dose was a critical factor is supported by the fact that blood levels of encainide and OD-methyl-encainide were significantly higher in patients who had an aggravation of arrhythmia than in those who were free of this effect. The extensive overlap in blood encainide values precludes their use for anticipating drug effect. Changes in electrocardiographic intervals were similar without predictive value of a toxic response. In a small series, Bren et al[18] reported that worsening of arrhythmia was associated with QT prolongation. In our experience no changes in either QRS width or QT-interval duration had predictive value.

In 7 patients worsening of arrhythmia occurred during exercise testing at a time when monitoring showed suppression of ventricular premature beats. Five of the 7 patients had received >200 mg/day of encainide. With such large doses, either the drug or its metabolites may excessively depress conduction velocity, prolong refractoriness and promote inhomogeneity in other electrophysiologic properties. These changes establish preconditions for arrhythmogenesis that results from exercise-promoted release of catecholamines.

The type and extent of underlying heart disease, the state of left ventricular function, and the presenting arrhythmia did not predict drug response. A systematic approach to drug testing such as that previously outlined[9,10] is essential to evaluate drug efficacy and reduce the incidence of adverse reactions during long-term therapy. Only 1 patient discontinued the drug because of an adverse effect during chronic maintenance.

We conclude that encainide is an effective agent for the treatment of malignant ventricular arrhythmias. However, there is a substantial risk for enhancement of arrhythmia that requires careful use of the drug. Recognition of the potential for worsening of arrhythmia, especially when doses exceed 200 mg/day, permits this drug to be used without substantial risk of serious injury. Response to encainide must be evaluated with both monitoring and exercise testing because aggravation of arrhythmia frequently occurs only during exercise. Its use should be reserved for patients with life-threatening ventricular arrhythmias refractory to conventional drugs.

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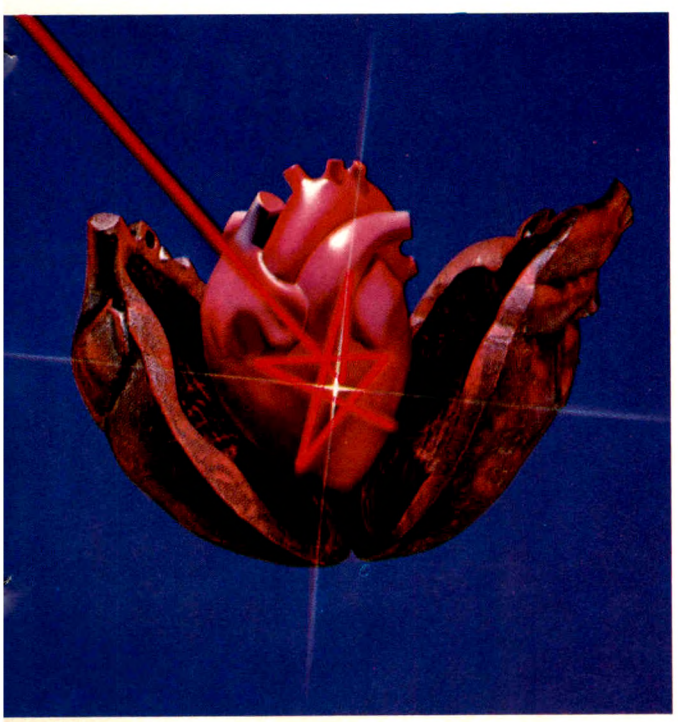

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†CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

*Angiotensin Converting Enzyme

Please see brief summary of prescribing information on last pages of this advertisement.

ACE*INHIBITOR

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CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

- **Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.**
- **Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.**
- **Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.**
- **The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.**

*Angiotensin Converting Enzyme

†Please see brief summary of prescribing information on last pages of this advertisement for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Data on file, Squibb Institute for Medical Research.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension — Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.
Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.
WARNINGS: Proteinuria — Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine — the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension — Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension — Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure — About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* — A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
Surgery/Anesthesia — If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.
Drug Interactions: *Hypotension: Patients on Diuretic Therapy* — Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release — Captopril's effect will be augmented by

 (Continued on next page.)

ontinued from preceding page)

ıtihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity — The sympathetic nervous system ay be especially important in supporting blood pressure in patients receiving ıptopril alone or with diuretics. Beta-adrenergic blocking drugs add some rther antihypertensive effect to captopril, but the overall response is less an additive. Therefore, use agents affecting sympathetic activity (e.g., anglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium — Give potassium-sparing diuretics or otassium supplements only for documented hypokalemia, and then with aution, since they may lead to a significant increase of serum potassium.

rug/Laboratory Test Interaction: Captopril may cause a false-positive urine st for acetone.

arcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year udies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any vidence of carcinogenic potential. Studies in rats have revealed no impair- ient of fertility.

sage in Pregnancy: There are no adequate and well-controlled studies in regnant women. Embryocidal effects were observed in rabbits. Therefore, aptopril should be used during pregnancy only if the potential benefit utweighs the potential risk to the fetus.

ursing Mothers: Captopril is secreted in human milk. Exercise caution when dministering captopril to a nursing woman, and, in general, nursing should be terrupted.

ediatric Use: Safety and effectiveness in children have not been established though there is limited experience with use of captopril in children from 2 onths to 15 years of age. Dosage, on a weight basis, was comparable to that sed in adults. Captopril should be used in children only if other measures for ontrolling blood pressure have not been effective.

DVERSE REACTIONS: Reported incidences are based on clinical trials volving about 4000 patients.

Renal — One to 2 of 100 patients developed proteinuria (see WARNINGS). enal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 2 of 1000 patients.

Hematologic — Neutropenia/agranulocytosis occurred in about 0.3% of aptopril treated patients (see WARNINGS). Two of these patients developed epsis and died.

Dermatologic — Rash (usually mild, maculopapular, rarely urticarial), often ith pruritus and sometimes with fever and eosinophilia, in about 10 of 100 atients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in bout 2 of 100 patients. A reversible associated pemphigoid-like lesion, and hotosensitivity have also been reported. Angioedema of the face, mucous embranes of the mouth, or of the extremities in about 1 of 100 patients — eversible on discontinuance of captopril therapy. One case of laryngeal dema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular — Hypotension in about 2 of 100 patients. See WARNINGS (ypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypo- ension on initiation of captopril therapy. Tachycardia, chest pain, and alpitations each in about 1 of 100 patients. Angina pectoris, myocardial ıfarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 000 patients.

Dysgeusia — About 7 of 100 patients developed a diminution or loss of taste erception; taste impairment is reversible and usually self-limited even with ontinued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, omiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizzi- ess, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and pares- hesias reported in about 0.5 to 2% of patients but did not appear at increased requency compared to placebo or other treatments used in controlled trials.

ltered Laboratory Findings: Elevations of liver enzymes in a few patients lthough no causal relationship has been established. Rarely cholestatic aundice and hepatocellular injury with secondary cholestasis have been eported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In nstances of rapid reduction of longstanding or severely elevated blood ressure, the glomerular filtration rate may decrease transiently, also resulting n transient rises in serum creatinine and BUN. Small increases in serum otassium concentration frequently occur, especially in patients with renal mpairment (see PRECAUTIONS).

)VERDOSAGE: Primary concern in correction of hypotension. Volume xpansion with an I.V. infusion of normal saline is the treatment of choice for estoration of blood pressure. Captopril may be removed from the general irculation by hemodialysis.

)OSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour efore meals. Dosage must be individualized; see DOSAGE AND ADMINIS- RATION section of package insert for detailed information regarding dosage n hypertension and in heart failure. Because CAPOTEN (captopril) is excreted rimarily by the kidneys, dosage adjustments are recommended for patients vith impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

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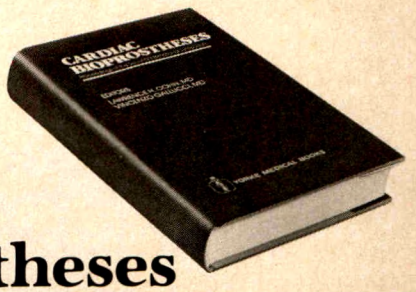

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

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Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

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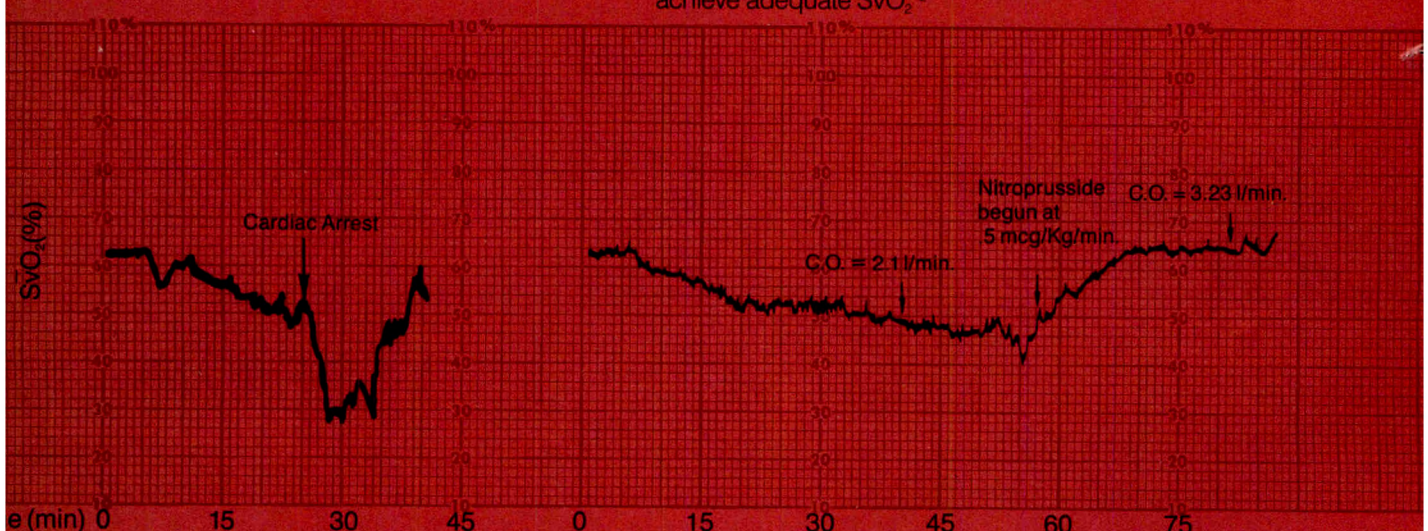
This postoperative patient with high systemic vascular resistance and low cardiac output required afterload reduction. Changes in cardiac output were directly reflected in changes of $S\bar{v}O_2$ and drug therapy was titrated to achieve adequate $S\bar{v}O_2$.[2]



1 Baele PI., McMichan JC., Marsh HM., and Southorn PA. "Continuous Monitoring of Mixed Venous Oxygen Saturation in Critically Ill Patients," **Anesthesia and Analgesia,** Vol. 61, No. 6, June 1982.

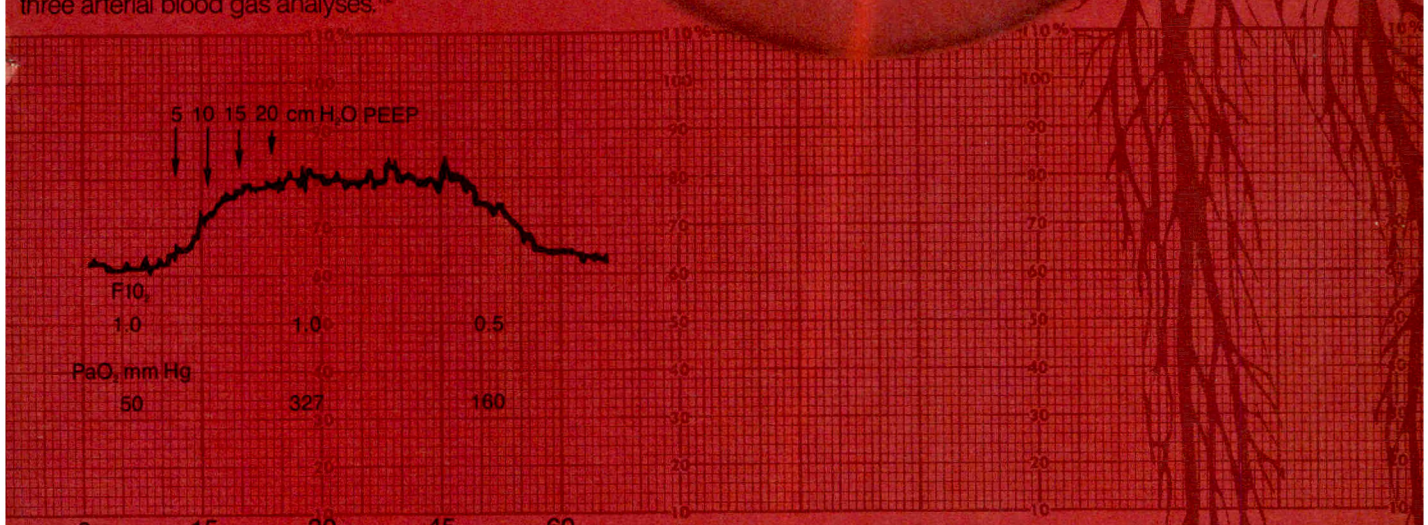
2 Schweiss J. (Ed). "Continuous Measurement of Blood Oxygen Saturation in the High Risk Patient," Vol. 1, (proceedings of a seminar held in conjunction with the Eleventh Annual Symposium of the Society of Critical Care Medicine), 1983.

3 Schmidt CR., Frank LP., Estafanous FG. "Utility of Continuous Pulmonary Artery Oximetry As An Early Warning Monitor in Cardiac Surgery Patients," paper presented at the 57th Congress of the International Anesthesia Research Society, New Orleans, March, 1983.

4 Watson C. "The PA Catheter As An Early Warning System," **Anesthesiology Review,** Vol. 10, No. 5, 1983.

Without continuous $S\bar{v}O_2$ monitoring, adjustment of PEEP and FIO_2 normally requires hours with numerous arterial blood gas analyses and cardiac output determinations.

In this case, PEEP was adjusted in 15 minutes and FIO_2 reduced within one hour with only three arterial blood gas analyses.[1,2]



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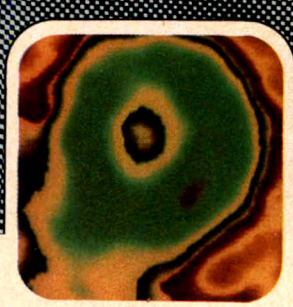
Thallium scintiscan after exercise, showing marked anterior wall perfusion defect (arrow) before angioplasty.[1]

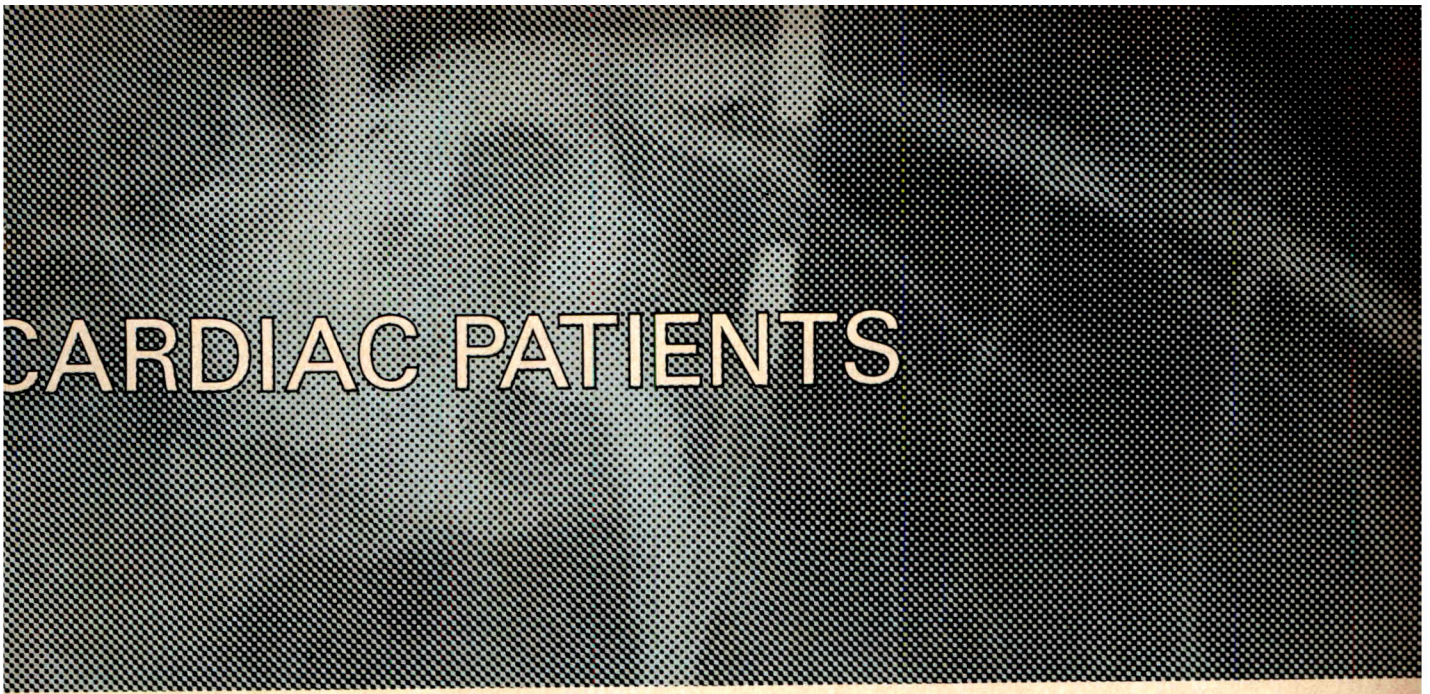


Postangioplasty thallium scintiscan showing no perfusion defect after peak exercise.[1]

FIRST THE BENEFITS OF PRIMARY MEASURES

Never before have physicians had so many resources for dealing effectively with cardiac disease. Now numerous cardiovascular medications are available—antianginal preparations, antihypertensives, diuretics, calcium antagonists, digitalis, quinidine, vasodilators. Besides these many agents, there are proven surgical procedures such as coronary bypass and valve replacement—and nonsurgical procedures such as angioplasty, which is fast becoming an accepted method of treating severe arterial stenoses.[1] The efficacy of angioplasty is illustrated in the above scintiscans. Yet, even with so many primary measures for improving the patient's cardiovascular status, secondary problems may adversely affect convalescence. One such problem may be excessive anxiety.[2]

References: 1. Vawter MH: *Continuing Education 1*7(2):17-24, Aug 1982. **2.**Wenger NK: *Cardiovasc Reviews & Reports 2*:1249-1260, Dec 1981. **3.** Kucharski A: *Am Fam Physician 1*7(3):154-157, Mar 1978.



SECOND THE BENEFITS OF ADJUNCTIVE ANTIANXIETY MEASURES

Anxiety in cardiac patients during recovery is a frequent response to symptoms such as chest pain, arrhythmias, breathlessness and weakness.[3] Often, anxiety can be allayed by supportive measures, such as encouraging the patient to express his fears openly, offering reassuring explanations for postcoronary symptoms and, when necessary, prescribing antianxiety medication.[3] For valid reasons, the medication often chosen is Valium® (diazepam/Roche). Its record of efficacy and safety is universally acknowledged. Little or no cardiotoxicity has been reported. Also, Valium is used with most primary cardiac medications. As with all CNS-acting agents, patients should be cautioned against drinking alcohol and against engaging in activities requiring complete mental alertness. Used judiciously, Valium can be a valuable adjunct to rehabilitative measures and can help the cardiac patient employ his own coping devices to good effect.

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Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.
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Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. or q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
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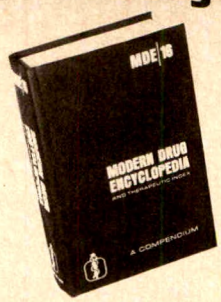

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REFERENCE 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

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PD-58-JA-1408-P-1(12-82)

Induction of Clinical Ventricular Tachycardia Using Programmed Stimulation: Value of Third and Fourth Extrastimuli

DAVID E. MANN, MD, JERRY C. LUCK, MD, JERRY C. GRIFFIN, MD, JOHN M. HERRE, MD, MARIAN C. LIMACHER, MD, SHARON A. MAGRO, PAC, NANCY W. ROBERTSON, CVNS, and CHRISTOPHER R. C. WYNDHAM, MD

Initiation of ventricular tachycardia (VT) by right ventricular extrastimulation was analyzed in 142 consecutive patients, 53 with electrocardiographically documented episodes of spontaneous VT or ventricular fibrillation (VF) and 68 with no spontaneous VT or VF; 21 patients with a history of sudden death but no documented arrhythmia were excluded from further analysis. All patients received 1 to 4 extrastimuli (S_2, S_3, S_4 and S_5) during pacing at fixed cycle lengths of 600 or 500 msec at 1 or 2 right ventricular sites. Clinical VT was reproduced by extrastimulation in 28 of 43 patients (65%) with sustained VT and in 0 of 10 patients with nonsustained VT. Clinical VT was induced by S_2 or S_3 in 16 patients and by S_4 or S_5 in 12 patients. Ventricular burst pacing reproduced clinical VT in 3 other patients. Nonclinical VT, which was most often polymorphic and nonsustained, was induced in 24 of 121 patients (20%), in 11 by S_2 or S_3 and in 13 by S_4 or S_5. Ventricular burst pacing induced nonclinical VT in 4 other patients.

In patients with spontaneous sustained VT, the use of S_4 and S_5 in the right ventricle increases the yield of inducible clinical VT compared with use of S_2 and S_3 alone, but at a cost of increased induction of nonclinical VT. Frequent induction of nonclinical VT limits the interpretation of the results of such stimulation in patients without previously documented VT.

(Am J Cardiol 1983;52:501–506)

Initiation of ventricular tachycardia (VT) by programmed stimulation has been used to plan effective therapy in patients with spontaneous episodes of VT.[1–5] However, to institute appropriate drug, pacemaker or surgical treatment, it is probably important that induced VT have the same mechanism as the spontaneous VT. This identity is manifested by similar morphology and cycle length of induced and spontaneous VT.

Most studies on the induction of VT using programmed stimulation have used up to 2 extrastimuli during multiple drive cycle lengths and at multiple right and left ventricular sites as well as short bursts of rapid ventricular pacing.[2–9] To increase the yield of inducible VT without resorting to left ventricular stimulation, we used third and fourth extrastimuli in the right ventricle. This report reviews our experience with this technique.

From the Cardiology Division, Methodist Hospital, Baylor College of Medicine, and the Veterans Administration Medical Center, Houston, Texas. Manuscript received March 3, 1983; revised manuscript received May 24, 1983, accepted May 25, 1983.

Address for reprints: Christopher R. C. Wyndham, MD, Director, Cardiac Electrophysiology, Mail Station F905, The Methodist Hospital, 6565 Fannin, Houston, Texas 77030.

Methods

Patients: The hospital records and electrophysiologic recordings of 142 consecutive patients who underwent ventricular extrastimulation with at least 1 extrastimulus from July 1980 to June 1982 were reviewed. All available records were obtained for each patient, and every attempt was made to obtain electrocardiographic documentation of any episodes of spontaneous VT or ventricular fibrillation (VF). Patients were divided into 2 groups. Group I consisted of 53 patients (44 men and 9 women, mean age 57 ± 11 years) who had ≥1 spontaneous episode of VT or VF documented by electrocardiography before electrophysiologic study (including 12-lead electrocardiography, ambulatory or exercise electrocardiography or a single-channel rhythm strip). Group II consisted of 68 patients (35 men and 33 women, mean age 46 ± 17 years) with no history of VT, VF or sudden cardiac death. Twenty-one patients with a history of sudden cardiac death but without electrocardiographic documentation of the causative arrhythmia were excluded from further analysis because the electrocardiographic morphology and cycle length

TABLE I Clinical Data

	Group I (n = 53)	Group II (n = 68)
Cardiac diagnosis		
CAD	38	11
CM	8	8
VHD	3	12
Cardiac tumor	2	0
No OHD	2	37
Indication for study		
Sustained VT	40	0
Nonsustained VT	10	0
VF	3	0
PSVT, AF, AFL	0	32
Conduction disease	0	10
Syncope, palpitations	0	26

AF = atrial fibrillation; AFL = atrial flutter; CAD = coronary artery disease; CM = cardiomyopathy; OHD = organic heart disease; PSVT = paroxysmal supraventricular tachycardia; VF = ventricular fibrillation; VHD = valvular heart disease (including mitral valve prolapse); VT = ventricular tachycardia.

TABLE II Induction of Clinical and Nonclinical Ventricular Tachycardia With Each Extrastimulus

	Group I			Group II	
Extrastimulus	n	CVT	NCVT	n	NCVT
S_2	53	8	1	68	1
S_3	46	8	7	26	2
S_4	31	5	7	18	4
S_5	16	7	1	12	1

n = number of patients who received each extrastimulus; CVT = number of patients in whom clinical ventricular tachycardia was induced with each extrastimulus; NCVT = number of patients in whom nonclinical VT was induced with each extrastimulus.

of the arrhythmia could not be established. The cardiac diagnoses in each group determined by history, physical examination, noninvasive testing and cardiac catheterization are listed in Table I. Coronary artery disease was the most frequent diagnosis in Group I, occurring in 38 patients (22 of whom were diagnosed by coronary arteriography); 34 patients had electrocardiographically documented remote (>1 month) myocardial infarction and evidence of regional wall motion abnormalities on 2-dimensional echocardiography or nuclear-gated wall motion study. Thirty-seven of the 68 patients in Group II had no heart disease. The most frequent reason for undergoing electrophysiologic study in Group II was supraventricular tachyarrhythmias (32 patients).

Definitions: The following definitions were used.

Nonsustained VT: VT of ≥6 beats that terminated spontaneously in <1 minute.

Sustained VT: VT that lasted >1 minute or required termination because of hemodynamic compromise. VF is grouped with sustained VT unless stated otherwise.

Induced VT: VT initiated by either extrastimulation or ventricular burst pacing at least once during electrophysiologic study.

Clinical VT: Spontaneous VT documented before electrophysiologic study. Induced VT was considered to be clinical VT if it was morphologically similar to spontaneous VT in every electrocardiographic lead recorded during electrophysiologic study (in general, similar morphology in lead V_1 and frontal-plane QRS axis within 45°), and the cycle length was similar to spontaneous VT (within 10% of spontaneous VT cycle length). The latter criterion was not used if spontaneous VT was documented only while the patient was taking class I antiarrhythmic drugs.

Nonclinical VT: Induced VT not identical, by the above criteria, to spontaneous VT.

S_1S_1: Basic paced cycle length.

S_2, S_3, S_4, S_5: First, second, third and fourth extrastimuli introduced during ventricular pacing at constant cycle length.

V_1V_2, V_2V_3, V_3V_4, V_4V_5: The coupling interval (in milliseconds) between the appropriate ventricular electrograms, measured at the first high-frequency crossing of the baseline.

Electrophysiologic studies: Electrophysiologic studies were performed in the postabsorptive, nonsedated state. Intracardiac electrode catheters were inserted through the femoral, brachial or subclavian veins. Programmed stimulation was performed using a digital stimulator (Bloom Associates, Ltd.) that delivered rectangular pulses of 2 msec duration at twice diastolic threshold. Surface leads I, II, III and V_1, and intracardiac electrograms were simultaneously recorded on light-sensitive paper at 100 mm/s paper speed (Electronics for Medicine VR-16 recorder).

Extrastimulation was performed in all patients at 1 or 2 right ventricular sites, either the right ventricular apex or septum. Two sites were used in 18 Group I patients (34%) and 18 Group II patients (26%) (not statistically significant [NS]). Left ventricular stimulation was not performed. Extrastimulation included introduction of S_2 through S_5 after 8 beats of ventricular pacing at a basic drive cycle length of 500 msec in 45 Group I and 39 Group II patients (NS); otherwise, 600 msec was used. Each successive extrastimulus was introduced decrementally until refractoriness was reached, then fixed at 20 ms beyond refractoriness while the next extrastimulus was introduced. In Group I patients, extrastimulation was continued until VT was induced or the protocol was completed. In Group II patients, who had no history of VT, fewer patients received the complete protocol. Extrastimulation using S_4 or S_5 was performed in 31 Group I (58%) and 18 Group II patients (26%) ($p < 0.001$). Ventricular burst pacing, consisting of 8 to 12 beats at decreasing cycle lengths down to 2:1 pacing non-

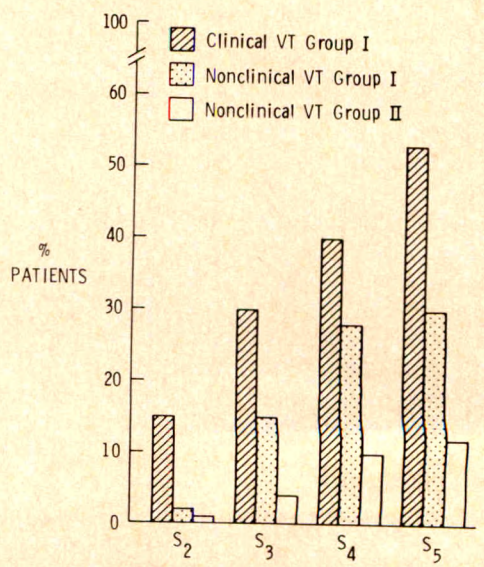

FIGURE 1. The cumulative yield of induced ventricular tachycardia (VT) (percentage of patients in each group with induced VT) with each added extrastimulus. With each additional extrastimulus, the rate of induction of clinical and nonclinical VT is increased in both groups.

capture, was then performed. Ventricular burst pacing was performed in 45 Group I (85%) and 64 Group II patients (94%) (NS). The minimum cycle length of ventricular burst pacing was <250 msec in 26 Group I (49%) and 37 Group II patients (54%) and 300 to 250 msec in the rest.

Induced VT was classified as clinical or nonclinical by the above definitions. The stimulation protocols that first initiated clinical and nonclinical VT in each patient were analyzed. The minimum attainable coupling intervals of the ventricular electrograms between each successive extrastimulus were measured.

Electrophysiologic studies were performed at least 48 hours after antiarrhythmic drugs had been discontinued. In patients with multiple studies in the drug-free state, only the first such was analyzed. However, in 11 of 14 patients whose spontaneous arrhythmia had only occurred while on a class I antiarrhythmic drug (procainamide, quinidine or disopyramide),[10] and who had no inducible VT in the control state, programmed stimulation was repeated after administration of intravenous procainamide (20 mg/kg) or, in 2 cases, on oral quinidine or disopyramide.

Statistical analysis: Numerical data were tested for significance by paired and unpaired t tests and by chi-square analysis. Values are given as mean ± standard deviation.

Results

Characteristics of spontaneous ventricular tachycardia: The most severe documented arrhythmia in Group I was VF in 3 patients, sustained VT in 40 patients and nonsustained VT in 10 patients. VF was documented by single-channel rhythm strips in all 3 patients. Sustained VT was documented by a 12-lead electrocardiogram in 30 patients, by a single-channel rhythm strip in 7 and by multiple-lead ambulatory or exercise electrocardiogram in 3. Nonsustained VT was documented by multiple-lead ambulatory or exercise electrocardiography in all 10 patients. Multiple distinct morphologies of VT were documented in 14 of 53 Group I patients (26%). Seventy-one different morphologies were documented in all 53 patients.

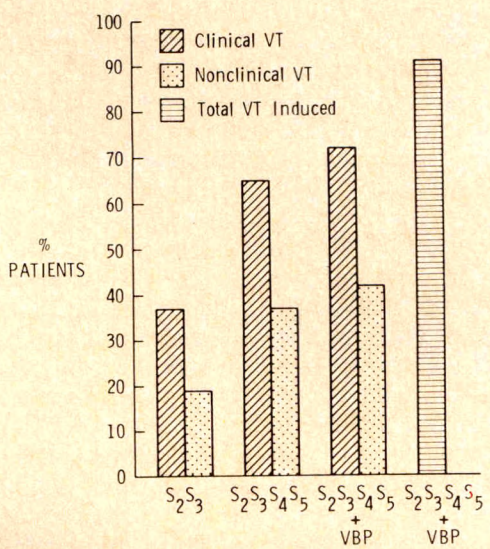

FIGURE 2. The cumulative yield of induced clinical and nonclinical ventricular tachycardia (VT) using progressively more "aggressive" modes of stimulation in 43 patients with a history of spontaneous sustained VT. Use of S_2S_3 alone, $S_2S_3S_4S_5$ and $S_2S_3S_4S_5$ plus ventricular burst pacing (VBP) are compared. The bar farthest to the right represents overall VT induction, ignoring the distinction between clinical and nonclinical VT.

Ventricular tachycardia induction: *Clinical VT:* VT morphologically similar to spontaneous VT was induced in 31 of 53 Group I patients (58%). Clinical VT was only induced in patients with the sustained form spontaneously (31 of 43 [72%]). Induced clinical VT was sustained in 26 patients and nonsustained, though of similar morphology and cycle length to spontaneous VT, in 5 patients. Clinical VT was not initiated in any patient whose spontaneous arrhythmia was nonsustained (0 of 10 patients). Considering only patients with spontaneous sustained VT (or VF), clinical VT was induced in 28 of 43 (65%) by extrastimulation, and in 3 of 43 (7%) by ventricular burst pacing alone.

Nonclinical VT: Nonclinical VT was induced in 28 of the 121 patients (23%). In Group I nonclinical VT was induced in 19 of 53 patients (36%), and was nonsustained in 11 and sustained in 8. In Group II nonclinical VT was induced in 9 of 68 patients (13%), and was nonsustained in 7 and sustained in 2. Nonclinical VT was induced in 24 of the 121 patients (20%) by extrastimulation and in 4 (3%) by ventricular burst pacing.

Comparison of modes of stimulation: Table II lists the number of patients in whom clinical and nonclinical VTs were induced with each extrastimulus. In Figure 1, these data are depicted graphically as the cumulative percentage of patients with VT induced after each extrastimulus was added. With each additional extrastimulus there is an increasing yield of induced clinical and nonclinical VT in both patient groups.

Figure 2 depicts VT induction in Group I patients with sustained spontaneous VT. Clinical VT was induced by S_2 or S_3 in 37% and nonclinical VT in 19% of these patients. With the addition of S_4 and S_5, clinical VT was induced in 65% and nonclinical VT in 37%. With the addition of ventricular burst pacing to extrastimulation, clinical VT was induced in 72% and nonclinical VT in 44%. The final bar in Figure 2 ignores the distinction between clinical and nonclinical VT and represents all induced episodes of VT. Thus, VT was induced in 91% of patients with the sustained arrhythmia spontaneously, using up to 4 extrastimuli and ventricular burst pacing in the right ventricle alone. Had S_4 and S_5 not been used, VT would have been inducible in only 65% of them from the right ventricle.

Drug-induced VT: In patients with spontaneous sustained VT, the spontaneous arrhythmia was documented on class I antiarrhythmic drugs in 23 of 43 patients (53%). Of these 23, clinical VT was induced in 12 (52%), and in 9 patients it was inducible in the drug-free state. Of the 14 patients in which VT could not be induced in the drug-free state, 11 were given a class I agent as described above and retested. Of these 11, in only 3 (27%) could VT then be induced.

Characteristics of induced ventricular tachycardia: Figure 3 is a comparison of the mean cycle lengths of clinical VT (spontaneous versus induced) and nonclinical VT in Groups I and II. As expected from the definition of clinical VT, there was no significant difference between the mean cycle length of spontaneous

TABLE III Morphologic Characteristics of Nonclinical Ventricular Tachycardia

NCVT Morphology	Group I	Group II	Total
Polymorphic nonsustained	6	6	12
Unimorphic sustained	6	2	8
Unimorphic nonsustained	5	1	6
Ventricular fibrillation	2	0	2
Totals	19	9	28

NCVT = nonclinical ventricular tachycardia.

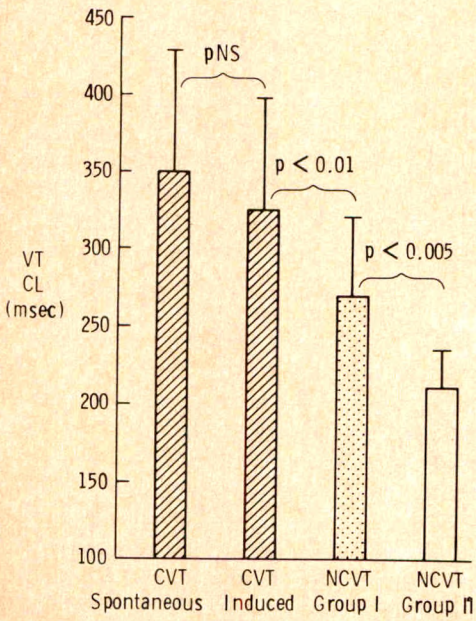

FIGURE 3. The mean cycle lengths (CL) of spontaneous ventricular tachycardia (VT) and induced clinical VT (CVT), as well as the mean CLs of induced nonclinical VT (NCVT) in both groups. NS = not significant.

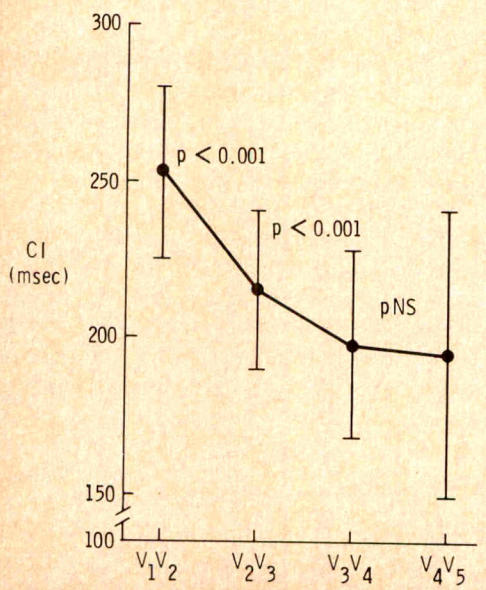

FIGURE 4. The mean minimum coupling intervals (CI) achievable by each pair of extrastimuli in 24 patients in whom all 4 extrastimuli were used and attained refractoriness. NS = not significant.

VT and induced clinical VT in group I (349.7 ± 78.5 versus 325.2 ± 73.4 msec, NS). Nonclinical VT in Group I patients had a significantly shorter mean cycle length than clinical VT (325.2 ± 73.4 versus 270.7 ± 51.3 msec, $p < 0.01$). Nonclinical VT in Group II had a still shorter mean cycle length than nonclinical VT in Group I (270.7 ± 51.3 versus 212.3 ± 23.4 msec, $p < 0.005$).

Induced clinical VT was most often unimorphic and sustained (26 patients). Induced clinical VT was unimorphic and nonsustained in 1 patient and polymorphic and nonsustained in 3. Of the 2 patients with spontaneous VF, 1 had no inducible VT or VF and 1 had what appeared morphologically to be induced VF (characterized by disorganized electrical activity in the intracardiac ventricular leads) that terminated spontaneously.

The morphologic characteristics of nonclinical VT are listed in Table III. The most common morphology was polymorphic and nonsustained; however, unimorphic forms occurred in both groups, although rarely (3 patients) in Group II. VF was induced in 2 patients in Group I in whom it had never occurred spontaneously and in no patients in Group II. Nonclinical VF was induced by S_4 in one case and by ventricular burst pacing at a cycle length of 230 msec in the other.

Analysis of minimum coupling intervals: The minimum achievable coupling intervals between the ventricular electrograms produced by S_2 through S_5 were averaged in 24 patients in whom all four extrastimuli were given and in whom each extrastimulus attained refractoriness. The results are illustrated in Figure 4. The mean coupling intervals decreased with each pair of extrastimuli, but in a decremental fashion (V_1V_2 253.1 ± 27.6 versus V_2V_3 215.4 ± 25.7, $p < 0.001$; V_2V_3 versus V_3V_4 198.3 ± 30.3, $p < 0.001$; V_3V_4 versus V_4V_5 194.6 ± 46.2 msec, NS).

Discussion

Programmed stimulation has been used in the electrophysiology laboratory to initiate VT in patients who have this arrhythmia spontaneously.[1–9] Drug treatment based on the results of acute drug testing using programmed stimulation is superior to empiric therapy in patients with inducible VT.[1–5] The ability to induce VT is crucial for successful surgical treatment of VT[11] and to test the reliability and safety of implanted tachycardia-terminating pacemakers.[12] More recently, programmed stimulation has been used in patients without a definite history of VT as a means to identify causative arrhythmias in patients with syncope[13,14] and to identify a group at high risk for subsequent sudden death after acute myocardial infarction.[15,16]

Pacing protocols used for induction of VT vary from laboratory to laboratory, making it difficult to compare the results of previous studies on the inducibility of VT. There is considerable variation in the number of extrastimuli used, the basic drive cycle lengths used and the sites of stimulation.[1–9] Changes in any of these factors may mean the difference between inducibility and noninducibility of VT. In a previous study using a protocol that included ≤2 extrastimuli and ventricular burst pacing at both right and left ventricular sites, VT was not inducible in 19% of patients with spontaneous

VT and was inducible from the left ventricle alone in 12%.[6] In a more recent, prospective study, again limited to 2 extrastimuli but without left ventricular stimulation, VT was induced in 71% of patients with spontaneous sustained VT and in 56% of patients with nonsustained VT.[7] Because left ventricular stimulation may increase the risk of electrophysiologic study by adding the risks of arterial catheterization and systemic embolism, and because chronic study of antiarrhythmic drugs is impractical in patients in whom VT is only inducible from the left ventricle, we used additional extrastimuli (S_4 and S_5) in the right ventricle in an attempt to increase the yield of inducible VT without necessitating left ventricular stimulation. In doing so, we have attempted to determine if induced VT matches spontaneous VT in morphology and cycle length, as it has been suggested that use of more than two extrastimuli increases the induction of nonclinical VT.[17]

In patients with spontaneous sustained VT, use of S_4 and S_5 increased the percentage of patients in whom clinical VT was induced from 37 to 65% over using S_2 and S_3 alone, but at a cost of increased induction of nonclinical VT (from 19 to 37%). Ventricular burst pacing further increased the induction of clinical and nonclinical VT to 72% and 44% of these patients. In our 10 patients who were studied for episodes of nonsustained VT, clinical VT was not inducible using our protocol. This contrasts with previous studies that, although showing lower inducibility of nonsustained VT as compared with sustained VT, still report inducibility in 56 to 62% of patients.[6,7] However, Denes et al[8] reported that clinical VT was not inducible in 6 patients studied with spontaneous nonsustained VT,[8] and Wellens et al[9] found that it could be induced in only only 1 of 15 patients with nonsustained VT. This variation in reported inducibility of nonsustained VT may, in part, be explained by differences in the definition of nonsustained VT. We defined nonsustained VT as 6 or more consecutive ventricular beats in order to prevent the interpretation of the repetitive ventricular response, which commonly occurs in normal and abnormal patients during programmed stimulation as nonsustained VT.[18]

The significance of nonclinical VT induction by programmed stimulation is uncertain. Reddy and Sartini[19] found a 50% incidence of nonclinical VT induction in patients with spontaneous sustained VT, and Mason and Winkle[3] found that nonclinical VT was induced in 16% of such patients. We found that nonclinical VT tends to be of significantly shorter cycle length than spontaneous VT, and is usually a nonsustained polymorphic arrhythmia. Nonclinical VT was more commonly induced in Group I patients, and this may, in part, reflect the more aggressive stimulation protocol used in these patients. However, more episodes of nonclinical VT tended to be unimorphic, sustained and of longer cycle length in Group I than Group II patients. It may be that nonclinical VT actually represented clinical VT that had not previously been documented, or different ventricular activation by the same reentrant circuit, a phenomenon shown to occur by endocardial catheter mapping.[20] Whether nonclinical VT in general is a marker of electrical instability, and thus a predictor of subsequent clinical events, or merely an artifact of the technique of programmed stimulation remains to be determined.

We analyzed the minimum attainable coupling intervals in our patients. Other than atrioventricular nodal refractory periods, cardiac refractory periods normally shorten as the cycle length of pacing shortens.[21] Introducing multiple extrastimuli during ventricular pacing at a fixed cycle length may be used to achieve shorter coupling intervals than those attainable by using single extrastimuli or ventricular burst pacing alone. In patients with VT originating from the left ventricle, critically short coupling intervals required for initiation of reentry may not be achievable by using only double extrastimuli in the right ventricle, presumably because of conduction delay between the site of pacing and the reentrant circuit. In such cases pacing closer to the reentrant circuit (that is, in the left ventricle) or use of more extrastimuli in the right ventricle might then induce VT.[17] Shorter coupling intervals are achievable by using S_4 and S_5 than by S_2 or S_3; however, there is no difference between the minimum V_3V_4 and V_4V_5 intervals. This suggests that there may be a limit to the degree that refractoriness may be shortened by added extrastimuli. However, there is yet a greater yield of induced VT with S_5 than with S_4, suggesting that critical shortening of local refractoriness at the pacing site is not the only factor involved.

Limitations of the study: The present study is retrospective, and may underestimate the inducibility of both clinical and nonclinical VT because of failure to complete the protocol and variations in the number of ventricular pacing sites used and the drive cycle lengths used. This is especially applicable to the Group II patients, in whom it was difficult to perform aggressive ventricular stimulation because of the possibility of inducing life-threatening arrhythmias of questionable clinical significance. Future prospective studies should not only address more stringently the issue of inducibility of nonclinical VT in patients without known spontaneous VT, but also should carefully compare the value of using multiple sites, different drive cycle lengths, and low versus high currents of stimulation. How the use of S_4 and S_5 will affect serial drug testing needs to be determined. Swerdlow et al[22] found that in patients in whom VT is induced with S_3 or less in the control state, use of S_4 during drug testing may be associated with a high drug failure rate, which may be spurious. Long-term follow-up of patients with induced nonclinical VT is needed to determine how often such morphologies of VT do subsequently occur spontaneously.

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Hemodynamic Effects of Encainide in Patients With Ventricular Arrhythmia and Poor Ventricular Function

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Gated cardiac scanning was used to evaluate the hemodynamic effects of encainide in 19 patients (1 woman) with complex ventricular arrhythmia and depressed left ventricular (LV) function (ejection fraction <45%). Patients were 36 to 80 years old (average 61). All were candidates for long-term encainide therapy after having failed with currently available antiarrhythmics. Sixty-three percent had congestive heart failure before they received encainide. All were evaluated in the hospital before encainide therapy by a gated cardiac scan performed at least 3 days after discontinuing all antiarrhythmic drugs. Patients received oral encainide in doses of 75 to 200 mg. Gated cardiac scans were repeated 1 to 2 weeks later when an 80% reduction in frequency of premature ventricular complexes was observed on a 24-hour Holter recording. No patient had worsening of congestive heart failure during encainide therapy. Encainide did not significantly affect ejection fraction, which averaged 22 ± 10% before and 25 ± 14% (SD) after encainide (difference not significant [NS]). Other hemodynamic variables, including heart rate, blood pressure, stroke volume and end-diastolic volume, remained unchanged during encainide therapy. Digoxin blood levels in 10 patients averaged 1.04 ± 0.43 before and 1.22 ± 0.47 mg/ml (NS) during encainide therapy. Thus, encainide given orally in clinically effective doses does not appear to have significant hemodynamic effects in patients with ventricular arrhythmia and depressed LV function. (Am J Cardiol 1983;52:507–511)

Currently available oral antiarrhythmics have negative inotropic effects.[1–5] Although this may be of little consequence in patients with normal ventricular function, patients with depressed ventricular function may experience worsening of symptoms or may develop congestive heart failure when given these drugs on a long-term basis.[4,5] Newly developed antiarrhythmics should therefore be evaluated for their hemodynamic effects before they are used in long-term trials. Encainide is a new benzanilide derivative with demonstrated antiarrhythmic efficacy that has been well tolerated in many clinical trials.[6–10] However, little information is available about its long-term hemodynamic effects, especially in patients with depressed left ventricular (LV) function.[10] We used gated cardiac blood pool imaging to evaluate the effects of encainide on LV function in patients with ventricular arrhythmia and depressed ejection fraction (EF).

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Materials and Methods

The subjects of this study are a subgroup of patients with complex and symptomatic ventricular arrhythmia who were considered for encainide therapy because of failure to respond to other antiarrhythmic drugs. Patients were selected for this study if they satisfied the following criteria: they had an EF <45% on a gated cardiac scan; they remained in a monitored cardiac unit with antiarrhythmics for 3 days before baseline study; those with congestive heart failure were on unchanged doses of digoxin and diuretics for at least 4 weeks before baseline evaluation and during the entire period of the study; and they did not have second- or third-degree heart block or a QRS duration >0.14 second. (One patient only had complete right bundle branch block with QRS of 0.12 second.)

Of the 23 patients who satisfied the above criteria, 4 were excluded before completion of the study, 3 because of technical difficulties with gated scanning and 1 because of new-onset sustained ventricular tachycardia 1 day after starting encainide. Table I shows the clinical features of the 19 patients participating in the study. Sixteen had coronary artery disease and 3 had dilated cardiomyopathy. Thirteen had clinical signs of congestive heart failure of class III or IV severity. All had frequent premature ventricular beats, ranging from 20 to 1355 per hour (median 279). All had frequent pairs and 18 had ≥1 salvos of nonsustained ventricular tachycardia per 24 hours.

TABLE I Clinical Characteristics of the Study Patients

Age (yr)	Underlying Heart Disease	CHF	Encainide Dose (mg)	Concomitant Medications
NYHA class II				
54	CAD	0	100	None
61	DC	0	75	None
48	DC	0	100	Diuretics
73	CAD (old MI)*	0	125	Diuretics, vasodilators
52	CAD (old MI)	0	100	Diuretics
NYHA class III				
70	CAD (recent MI)†	+	100	Digoxin, diuretics, vasodilators
67	CAD (old MI)	+	100	Digoxin, diuretics, vasodilators
62	CAD (old MI, LV aneurysm)	+	75	Digoxin
52	CAD (old MI)	+	75	Digoxin, diuretics
65	CAD (old MI)	+	200	Digoxin, diuretics, vasodilators
51*	CAD	+	100	Digoxin, diuretics
75	CAD (old MI)	0	100	Propranolol
NYHA class IV				
68	CAD (old MI)	+	75	Digoxin, diuretics, vasodilators
80	CAD (old MI)	+	150	Digoxin, diuretics, vasodilators
53	CAD (old MI)	+	100	Digoxin, diuretics
59	CAD (old MI)	+	100	Digoxin, diuretics, vasodilators
60	CAD (old MI)	+	100	Diuretics
36	CAD (recent MI)	+	100	Digoxin
70	DC	+	100	Digoxin, diuretics

* More than 3 months old.
† One to 3 months old.
CAD = coronary artery disease; CHF = congestive heart failure; DC = dilated cardiomyopathy; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association functional classification; + = present; 0 = absent.

Patients underwent a baseline evaluation that included clinical examination, with special attention to signs and symptoms of congestive heart failure; gated equilibrium cardiac blood pool scans; and routine hematologic and biochemistry laboratory work, resting 12-lead ECG and 24-hour Holter recordings. In addition, 10 ml of venous blood were obtained before their daily dose of digoxin to determine plasma concentrations.

All patients were then given encainide orally in doses of 25 mg every 8 hours. The dose was increased every 3 days to a maximum of 200 mg/day or until the patient demonstrated 80% reduction of the frequency of premature ventricular complexes on serial 24-hour Holter recordings without side effects. Encainide doses were 25 mg every 6 hours, 50 mg every 8 hours, or 50 mg every 6 hours.

Clinical examination, gated blood pool scanning, electrocardiography and routine hematology and biochemistry laboratory work were repeated 1 to 2 weeks after starting oral encainide therapy and digoxin and encainide blood levels were measured again.

Twenty-four-hour Holter recordings were performed using Oxford Medilog AM dual channel recorders 4-24/2. Analysis of the tapes was performed by a trained nurse using a Reynolds Pathfinder high-speed analyzer equipped with a printer interface module to allow printouts of the hourly totals of all QRS, all premature aberrant beats, pairs and salvos of ≥3 premature ventricular complexes. The pathfinder mode of action and its accuracy have been described.[11]

Digoxin plasma concentration was determined using a tritium radioimmunoassay method.[12] Plasma concentrations of encainide and its 2 common metabolites, O-demethyl encainide (ODE) and 3 methoxy ODE, were determined using high-pressure liquid chromatography.[13]

Data acquisition of the gated cardiac study was done with parallel low-energy collimation of a Picker mobile camera interfaced to an Informatek Simis 3 computer. Data were acquired in 16 equally timed frames of 64 × 64 matrices in the left anterior oblique position after in vivo labeling of the patient's red blood cells with 20 mCi of technetium-99m O_4^-. In the left anterior oblique position that showed the septum to best advantage, an additional 15° caudal tilt of the camera head was used to further facilitate atrioventricular separation. Arrhythmia filtering was obtained by establishing a tolerance window about the mean RR interval, rejecting cycles that varied more than 10% from the mean cycle length. Data were recorded over an imaging interval of 15 minutes or for a total accumulation of 5 million counts, depending on which limit was first reached. At the end of the acquisition, a 10-ml sample of the patient's blood was withdrawn and counted for 1 minute with the syringe in the direct contact with the collimator face.

For the analysis the data were normalized to ensure equal counts from each of the 16 frames. The raw data were smoothed with a 9-point filter and modified by threshold background subtraction. The second derivative approach helped determine the edges of the left ventricle.[14] The EF was calculated from the time-activity curve of the reconstituted cardiac cycle generated from a region of interest placed over the left ventricle by the operator. The stroke volume value in counts (LV end-diastolic counts LV end-systolic counts) was then converted into a volume equivalent in milliliters. This was done through division of the count stroke volume by the counts per milliliter of syringe blood. This syringe count value had previously been corrected by an attenuation factor to compensate for the different counting geometry and attenuation of the blood sample and the left ventricle.[15] Subsequently, end-diastolic volume was calculated from the EF and stroke volume.

To test the reproducibility of the LVEF, as measured by nuclear ventriculography in our laboratory, a sample of 20 patients (15 men, 4 women, average age 60 years) with heart disease underwent gated blood pool scanning twice within 20 minutes. Patients were allowed to walk around between the acquisitions and each acquisition was analyzed by a different operator. The 2 test results for EF were then assessed for their reproducibility using the product normal correlation coefficient, and the 95% two-tailed confidence intervals for this relationship were plotted as previously described.[16]

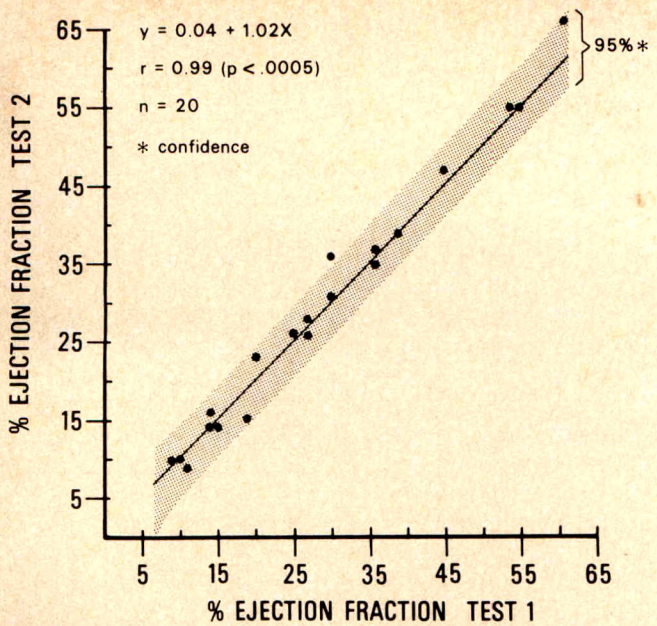

FIGURE 1. Linear regression analysis with 95%, 2-tailed confidence interval of variability for ejection fraction (EF). These measurements of EF were obtained from gated equilibrium blood pool scanning performed twice within 30 minutes.

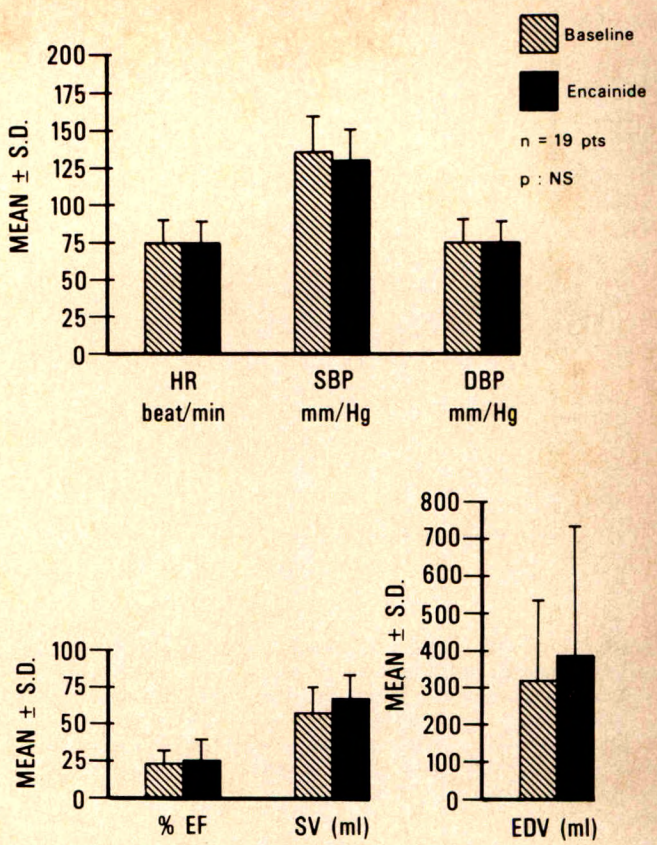

FIGURE 2. Means and standard deviations (SD) of hemodynamic indexes measured at basesline and during encainide therapy for 19 patients selected in the study. Statistical analysis using a paired *t* test did not show significant difference between measurements. DBP = diastolic blood pressure; EDV = end-diastolic volume; EF = ejection fraction; HR = heart rate; SBP = systolic blood pressure; SV = stroke volume.

Figure 1 shows the reproducibility of EF in our institution. The EF showed a high reproducibility (r = 0.99) and a relatively narrow 95% two-tailed confidence band. The maximum variation in EF between test 1 and test 2 was 5%.

Data obtained before and during treatment with encainide were analyzed by paired *t* tests to detect significant differences in heart rate, blood pressure, ejection fraction, stroke volume, end-diastolic volumes and digoxin plasma concentration.

Results

Hemodynamics: In the group as a whole, there was no significant change in heart rate, systolic or diastolic blood pressure, EF, stroke volume or end-diastolic volume before or after oral encainide (Fig. 2).

Individual values for EF at baseline and during oral encainide therapy were plotted on a graph representing the 95% two-tailed confidence band obtained as described in the Methods (Fig. 3). Most values fell within the 95% confidence band for variability, with only 4 patients showing a statistically significant increase and no patient showing a significant reduction in EF while receiving encainide.

Digoxin blood levels: Digoxin blood levels obtained in 10 patients before and 1 and 2 weeks after starting encainide therapy in various dosages were not significantly changed. The mean digoxin blood level at baseline was 1.04 ± 43 ng/ml (LSD) and at the end of 1 to 2 weeks of encainide, 1.22 ± 0.47 ng/ml (± SD) ($p > 0.25$).

Encainide plasma concentrations: The plasma concentrations and encainide and its 2 major metabolites after oral administration showed a marked interpatient variation, with little correlation of dosage: plasma concentrations of encainide ranged from 0 to 1110 ng/ml (mean 166), ODE from 0 to 665 ng/ml (mean 194) and 3 methoxy ODE from 0 to 916 ng/ml (mean 189).

Side effects: One patient who had been excluded 24 hours after starting encainide because of new-onset sustained ventricular tachycardia was later found not to have a detectable encainide or encainide metabolite in the plasma at the time of ventricular tachycardia. Another patient developed sustained ventricular tachycardia shortly after completing the 2-week period of study. Both were successfully resuscitated, but were never rechallenged with encainide.

Two patients demonstrated sinus pauses (≤2 seconds in duration) during encainide therapy, but remained asymptomatic. None of the the patients showed significant worsening of clinical signs or symptoms of congestive heart failure during the 2 weeks of the trial, although subtle changes may have been difficult to detect in class IV patients because of already severe symptoms and poor response to medication. Routine hematologic and biochemistry laboratory evaluation did not show any significant changes during administration of encainide.

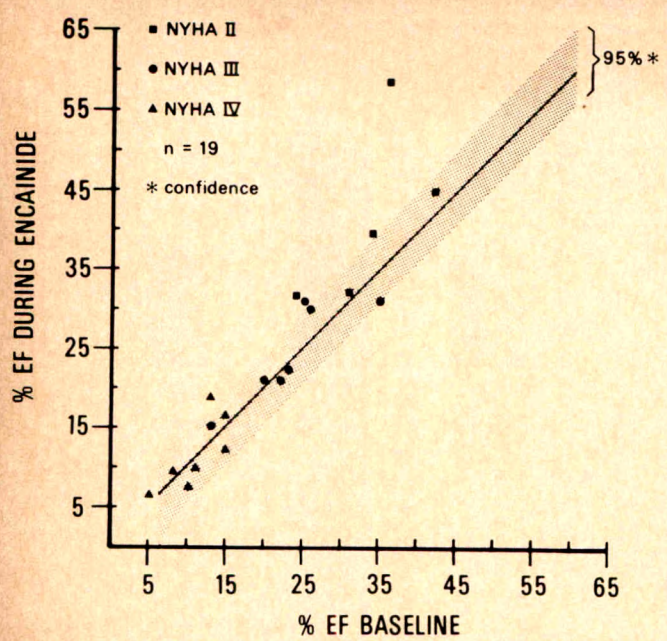

FIGURE 3. Ejection fractions (EF) before and during encainide. Using as background the graph described in Figure 1, we plotted on the abscissa baseline values for EF measured from gated equilibrium blood pool scanning of the 19 patients of Group II who received encainide. Data obtained during encainide therapy were plotted on the ordinates. Patients in New York Heart Association (NYHA) class II are represented by **squares,** those in class III by **circles** and those in class IV by **triangles.**

Discussion

EFs measured by gated cardiac blood pool scans correlate well with those obtained at cardiac catheterization.[17] However, to serially evaluate the effect of 1 drug on any index of cardiac function, the reproducibility of the test must first be defined. Our data suggest that the reproducibility of EF as measured by gated scans in our institution is excellent (Fig. 1). Using the technique we had previously used to test reproducibility of frequency of premature ventricular complexes on Holter monitor recording,[16] we demonstrated that there was no significant change in EF after 1 to 2 weeks of steady-state oral dosage of encainide in patients with depressed LV function; nor did we observed any worsening of clinical congestive heart failure over this period. This is especially significant because the majority of our patients had congestive heart failure of New York Heart Association class III or IV severity. DiBianco et al[10] reported similar observations in a smaller number of patients with severe ventricular arrhythmias, some of whom also had depressed LV function. Anderson et al[18] also found that encainide was well tolerated; they did not note adverse hemodynamic effects in 22 patients with refractory ventricular arrhythmias.

In the presence of arrhythmias, variation of the RR interval may result in a less-than-optimal reconstruction of an idealized average cycle. Error may be somewhat minimized, however, by rigid arrhythmia filtering to look at a more uniform pattern of cardiac contractions. In 1 patient who showed markedly improved EF after encainide therapy, the apparent increase in EF may have reflected, in part, the enhanced accuracy of the gating technique in the presence of a more uniform heart rate rather than a true improvement in LV function.

The lack of significant changes in heart rate and blood pressure during encainide therapy has been demonstrated elsewhere.[10,16] We did not report here the significant electrocardiographic changes in our patients because they have been well described.[8–10,16,18]

Digoxin blood levels showed a minimal, but not statistically significant, increase during encainide therapy. Furthermore, none of our patients developed symptoms or signs of digitalis toxicity. Encainide therapy may therefore present an additional advantage in patients with ventricular arrhythmia who are also taking digoxin, because other antiarrhythmics may significantly increase digoxin plasma concentration and, in some cases, lead to digitalis toxicity.[19]

Encainide and its 2 metabolites, ODE and 3 methoxy ODE, showed marked interpatient variation and a poor correlation with oral dosage in our study. This could be a result of variable liver metabolism of the drug. Roden et al[8] also noted intersubject variation in pattern of metabolism of encainide—1 of 11 patients in their series did not form ODE. An important reason for the apparent lack of correlation between encainide or any of the known metabolites with dosage or clinical response is that 1 or more of encainide metabolites contribute to antiarrhythmic activity.[8] Anderson et al[18] made similar observations in their patients who received steady-state oral doses of encainide. The mean plasma concentration of encainide and its 2 major metabolites in their patients after control of ventricular arrhythmias were similar to those in our patients.

Acknowledgment: We thank Professor Robin Shanks of Queen's University in Belfast, Ireland, and Dr. Raymond Woosley of Vanderbilt University in Nashville, Tennessee, for their measurements of encainide plasma concentrations.

We also thank Josée Roy, RN, and Ruth Ripley, RN, for their valuable assistance in the data collection and Drs. David Stubington, Maurice McGregor and Allan Sniderman of the Royal Victoria Hospital for their help in reviewing the manuscript.

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Circulatory Autoregulation in Chronic Congestive Heart Failure: Responses to Head-Up Tilt in 41 Patients

SPENCER H. KUBO, MD, and ROBERT J. CODY, MD

To evaluate mechanisms that regulate the response to postural change in patients with chronic congestive heart failure (CHF), the hemodynamic and vasoactive hormonal responses to head-up tilt were examined in 41 patients. Peripheral venous pooling was present in only 18 patients and was inversely correlated with baseline pulmonary wedge pressure. Baseline supine hemodynamic indexes of these 18 patients indicated less severe CHF compared with those of the 23 patients who did not demonstrate venous pooling. The 18 patients with intact afferent pooling also had lower levels of plasma renin activity and demonstrated increases in both plasma renin activity and norepinephrine on tilt; these reflex increases in vasoactive hormones were not seen in the 23 patients with severe CHF. Overall, 3 patterns could be identified. Of the 18 patients with venous pooling, 12 maintained many of the elements of normal postural response, with increases in systemic vascular resistance and circulating norepinephrine that maintain blood pressure constant. Six patients did not increase resistance in response to peripheral venous pooling and had major decreases in blood pressure analogous to idiopathic orthostatic hypotension. The larger group of 23 patients with more severe CHF did not have peripheral venous pooling and, hence, no afferent stimulus for reflex changes. Thus, the hemodynamic and neurohormonal responses to head-up tilt in CHF are heterogeneous and may be influenced by the severity of disease. The abnormalities of response may reflect the progression of vascular adaptation with loss of myocardial pump function and are important in terms of the pathophysiology and treatment of chronic heart failure.

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There is an extensive literature describing the hemodynamic response to vasodilator therapy of chronic congestive heart failure (CHF).[1,2] However, few data are available regarding the hemodynamic response to assuming the upright posture, a response first identified as abnormal in CHF by Abelmann and Fareeduddin.[3] Head-up tilt normally results in significant pooling of blood in the venous capacitance vessels, resulting in decreased filling pressures and cardiac output (Fig. 1). This stimulates a reflex increase in heart rate and systemic vascular resistance[4–6] and activation of the renin-angiotensin-system[7,8] and sympathetic nervous system[9,10] to prevent orthostatic hypotension. The uniformity of this response and its regulating mechanisms in patients with CHF have not been fully identified. In the present study, we examined the hemodynamic and vasoactive hormonal responses to head-up tilt in 41 patients with severe chronic CHF to determine the characteristics of the reflex changes that protect circulatory integrity. To place the CHF response to tilt in appropriate context, this was also compared to the response of idiopathic orthostatic hypotension, where baroreceptor regulation is totally deficient.

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Methods

Forty-one patients with severe chronic CHF (New York Heart Association functional class III or IV) were studied. Thirty-four were men and 7 were women, aged 20 to 77 years. Sixteen patients had an idiopathic dilated cardiomyopathy and 25 patients had a cardiomyopathy secondary to coronary artery disease. All patients were hospitalized in a metabolic ward and maintained on a 100-mEq/day sodium diet. Previous vasodilator therapy was discontinued for at least 4 days before this study. Most patients were maintained on digoxin and diuretic therapy without alteration of dosage. All other cardioactive drugs were discontinued.

Hemodynamic studies were performed after an overnight fast, withholding the morning dose of diuretic. Heart rate was monitored from a precordial lead. Arterial blood pressure was continuously recorded by placing a cannula in a radial artery and was expressed as the electronically damped mean. Right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output were measured with a thermodilution catheter. Cardiac output was determined

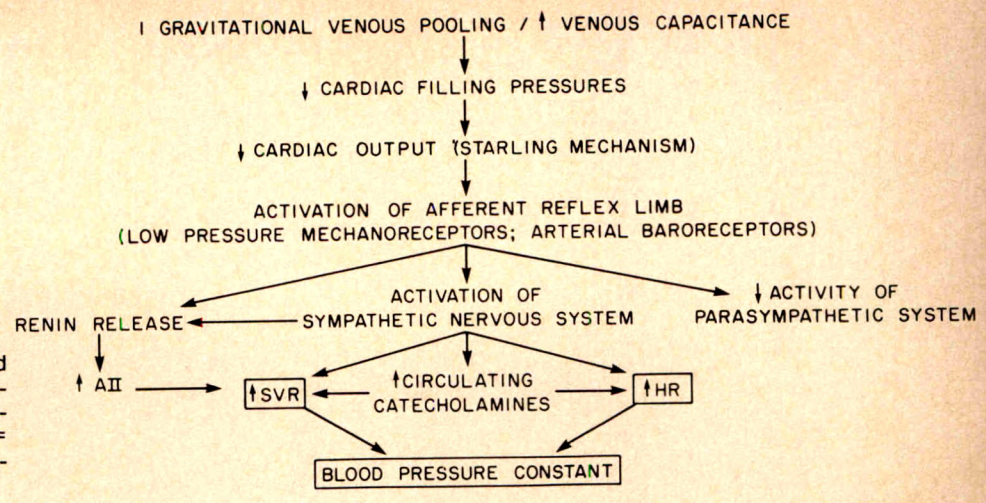

FIGURE 1. The normal hemodynamic and neurohormonal responses to the gravitational stress of upright posture and venous pooling. AII = angiotensin II; HR = heart rate; SVR = systemic vascular resistance.

in triplicate and corrected for body surface area. Systemic vascular resistance was calculated as (mean arterial pressure − mean right atrial pressure/cardiac output) × 80. Pressure recordings were obtained by electronic damping and simultaneously recorded on a strip-chart recorder. After catheter placement, the patients remained in the supine position for 1 hour. Baseline measurements were recorded twice, 30 minutes apart. Upright hemodynamics were determined by tilting the patient on an electric table to 60° for 10 minutes, a level that provides maximal hemodynamic response to venous peripheral pooling.[5] Pressure transducers were attached to a swivel on the table so that they remained at the same level of the atria and maintained the phlebostatic level described by Rushmer[6] during tilt.

For comparison to the CHF group, the hemodynamic response to tilt for normal subjects and patients with idiopathic orthostatic hypotension was summarized from previous data.[11,12]

Plasma renin activity was estimated by radioimmunoassay of angiotensin I generated in vivo.[13] In normal subjects, the range for plasma renin activity is based on a nomogram relating to the 24-hour urinary excretion of sodium; this relationship is not preserved in patients with CHF, but for normal persons with a moderate sodium intake, the upper limit of normal is 6 ng/ml/h. Plasma norepinephrine and epinephrine levels were determined by radioenzymatic assay.[14] Normal values are 165 ± 66 and 23 ± 19 pg/ml, respectively.

Correlations were obtained by linear regression analysis. A Student t test was used for comparison of mean supine values and a paired t test was used to evaluate the changes between supine and tilt values, as each patient served as his own control. Values represent the mean ± 1 standard error of the mean.

Results

Hemodynamic response to head-up tilt: The hemodynamic response to tilt in 7 normal subjects is diagrammed in Figure 2. Tilt caused marked peripheral venous pooling, as reflected by a 22% reduction of cardiac index. Because of reflex increases in heart rate (22%) and systemic vascular resistance (33%), there was no change in arterial pressure. In 8 patients with idiopathic orthostatic hypotension, tilt caused a more marked fall in cardiac index (−37%). Due to the blunted responses, the increases of heart rate (5%) and systemic vascular resistance (9%) were insufficient to prevent a

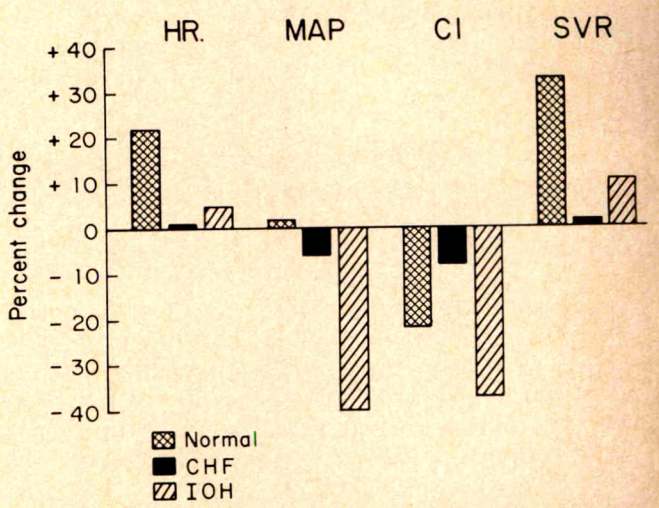

FIGURE 2. The overall qualitative responses to head-up tilt in 3 groups of patients: normal subjects, patients with congestive heart failure (CHF), and patients with idiopathic orthostatic hypotension (IOH). In normal subjects, mean arterial pressure (MAP) is maintained in the presence of the gravitational decrease of cardiac index (CI), due to the reflex increase of heart rate (HR) and systemic vascular resistance (SVR). In chronic CHF, the afferent stimulus of the reduction of CI is not present in the overall group of patients, so that HR and SVR do not change. In patients with IOH, there is an inadequate increase of HR and SVR to the gravitational stress of the CI reduction. Therefore, a marked reduction of MAP occurs.

marked orthostatic reduction of blood pressure (−40%). The response of CHF patients was unlike that of the normal or idiopathic orthostatic hypotension groups. Overall, tilt caused only an 8% reduction in cardiac index, with only small increases in heart rate (2%) and systemic vascular resistance (2%) and a small decrease in blood pressure (−6%). To determine the uniformity of the response to postural change in terms of the ability to stimulate reflex regulatory mechanisms, we evaluated individual tilt responses in the CHF group.

Afferent peripheral venous pooling in congestive heart failure: The extent of the decrease in cardiac index (i.e., peripheral venous pooling) was evaluated as a function of supine cardiac filling pressures. The de-

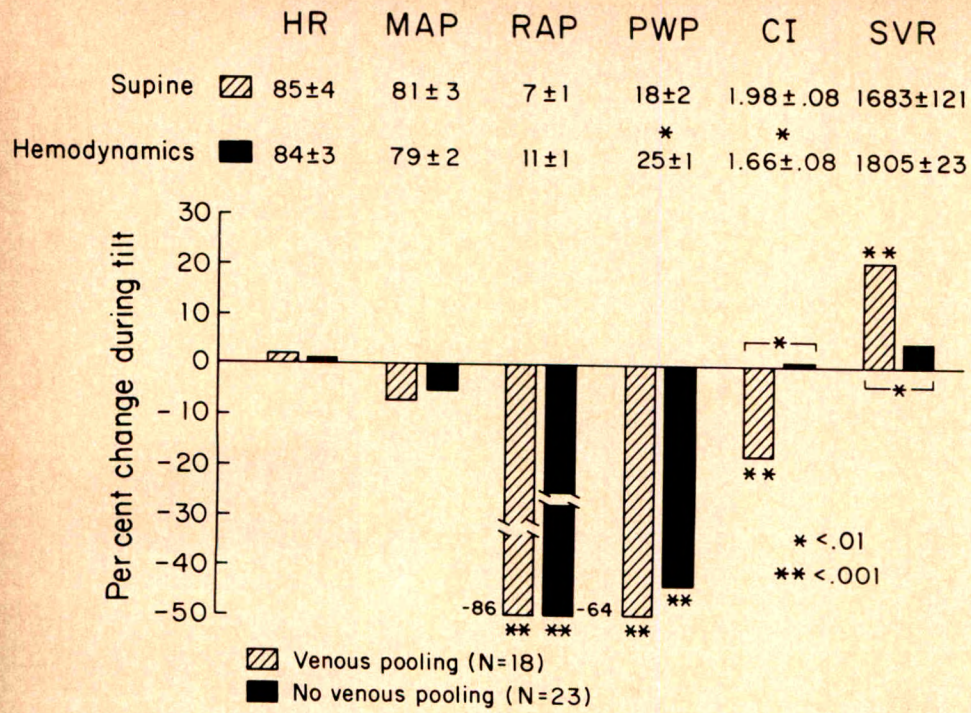

FIGURE 3. Upper portion, the supine hemodynamics for patients with congestive heart failure (CHF) with venous pooling compared with CHF patients without venous pooling. There was a statistically significant difference of supine pulmonary wedge pressure (PWP) and cardiac index (CI) for the 2 groups, and the differences of right atrial pressures (RAP) were small but statistically significant ($p < 0.05$). Although there was a difference in supine systemic vascular resistance (SVR) (1683 versus 1805), this did not achieve statistical significance. **Lower portion,** during head-up tilt, there were comparable reductions of RAP and PWP compared with respective supine values. By definition, the magnitude of reduction of CI during tilt was different for the 2 groups. For the group with venous pooling, mean arterial pressure (MAP) did not change because of the significant (19%) increase of SVR. This reflex increase was sufficient to avert orthostatic hypotension. In the patients with no venous pooling, there was no afferent stimulus for increase of SVR. There was no significant change of heart rate (HR) for either subgroup.

crease in cardiac index during tilt was inversely correlated with baseline pulmonary capillary wedge pressure ($r = -0.450$; $p < 0.01$) and was most apparent in patients with a wedge pressure <15 mm Hg. However, there was wide scatter along the regression line, and the presence of pooling during head-up tilt was not uniform, since 23 of 41 patients did not have a substantial fall (>10%) in cardiac index. This suggests that the first major abnormality in baroreceptor regulation was the presence or absence of peripheral venous pooling. Figure 3 shows the hemodynamic responses of the 18 patients who demonstrated afferent peripheral venous pooling and for the 23 patients who did not. In the baseline supine position, there was no significant difference between the two groups in heart rate, mean arterial pressure or systemic vascular resistance. However, the differences in baseline pulmonary capillary wedge pressure and cardiac index were highly significant. The difference in right atrial pressure was also significant ($p < 0.05$). Thus, the supine hemodynamic indexes of the group of patients with relatively intact venous pooling indicated less severe CHF compared with those of the larger group of patients without pooling.

The hemodynamic response to tilt was also different for these two groups (Fig. 3). In response to peripheral venous pooling ($n = 18$), there was a significant increase of systemic vascular resistance sufficient to prevent orthostatic hypotension. Despite similar reductions in cardiac filling pressures, the patients without peripheral pooling ($n = 23$) did not stimulate a compensatory increase in systemic vascular resistance so that only a small reduction of mean arterial pressure occurred. For both groups, there was a notable absence of reflex tachycardia.

Vasoactive hormonal response to tilt: For the total CHF group, there was a wide range of baseline plasma renin activity in the supine position without a significant change during head-up tilt (Fig. 4). When subdivided according to the presence or absence of peripheral pooling, supine plasma renin activity of patients who had venous pooling was significantly lower than that in patients without pooling (4.3 ± 1 versus 16.4 ± 4.3, $p < 0.02$), indicating less activation of the renin-angiotensin system. In addition, the change in plasma renin activity during tilt was different; patients with pooling showed a 40% increase ($p < 0.01$) and patients without pooling showed a minimal (7%) decrease.

Catecholamine levels were measured in 25 patients (Fig. 5). For the total group, there was a wide range of levels of norepinephrine in the baseline supine position, but no increase during head-up tilt. There was no difference in supine values for the pooling versus non-pooling groups. However, the pooling group did have a significant increase (28%) in norepinephrine levels ($p < 0.01$), whereas norepinephrine levels did not increase in the non-pooling group. For epinephrine, there was no difference in supine levels for the 2 groups, nor any significant change during tilt for either group. The changes in norepinephrine and epinephrine levels were not concordant; an increase in 1 catecholamine was not always associated with an increase in the other. Furthermore, the catecholamine response was not correlated with hemodynamic changes during tilt.

Hemodynamic patterns during head-up tilt in chronic heart failure: The hemodynamic response to tilt in patients with relatively normal peripheral venous pooling could be further divided into two subsets (Fig. 6). In 12 patients (Group A), blood pressure remained

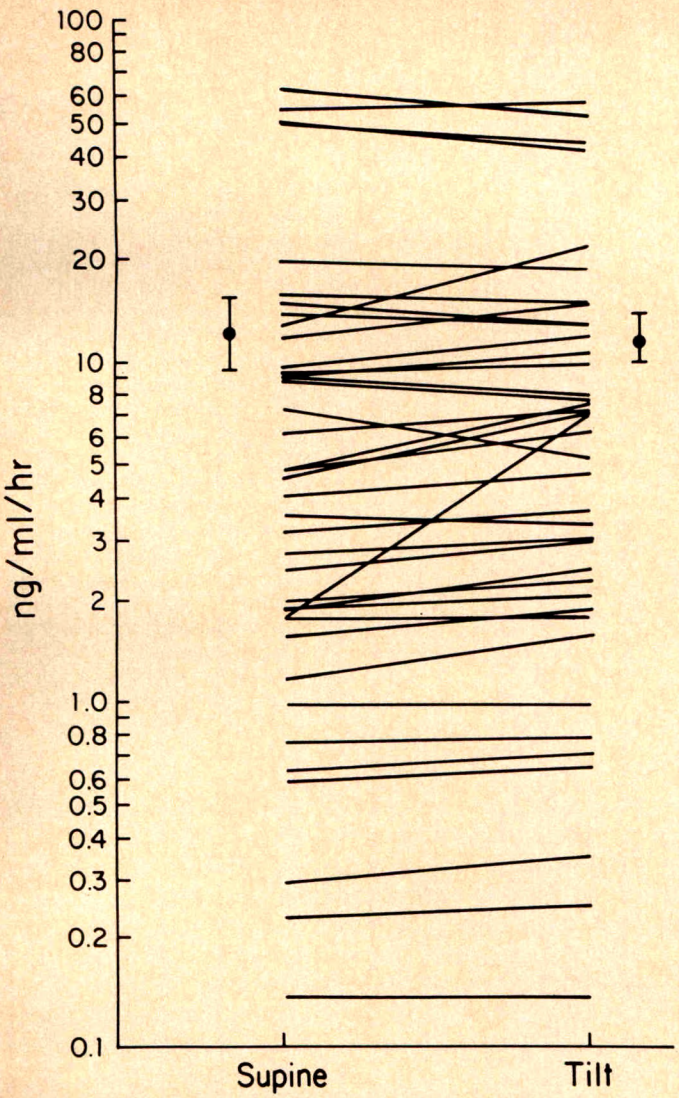

FIGURE 4. Despite a wide range of supine plasma renin activity (0.14 to 66 mg/ml/h), there was no significant increase in plasma renin activity for the 41 patients with congestive heart failure.

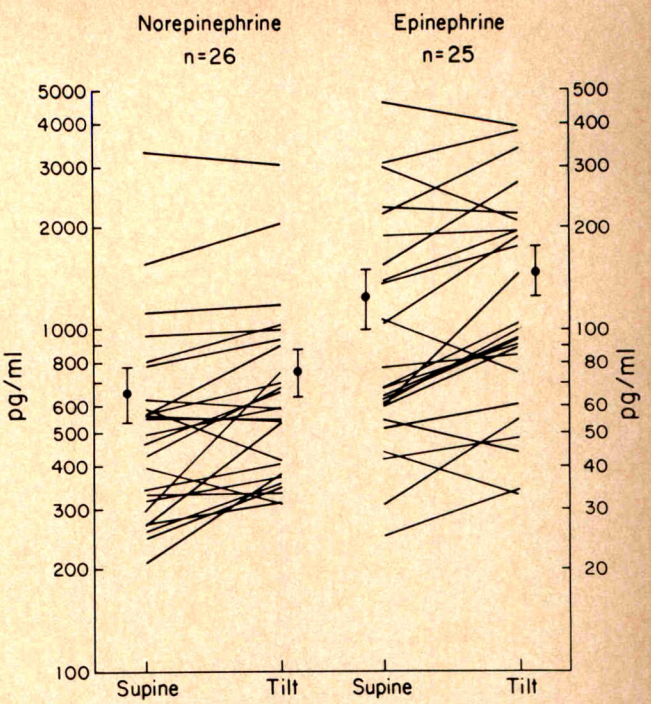

FIGURE 5. Plasma catecholamine levels were available for most of the patients in this study. Overall, there was no trend of response for norepinephrine and epinephrine during head-up tilt.

constant during tilt despite significant reductions of cardiac index, due to a significant reflex increase of systemic vascular resistance. In contrast, in 6 patients with similar reductions of cardiac index and filling pressures (Group B), marked orthostatic hypotension developed during tilt (−30%) because of an inadequate increase of systemic vascular resistance. There were no differences in supine hemodynamic indexes or supine vasoactive hormones between these subsets. The increase of plasma renin activity in the overall group of 18 patients was no longer significant when patients were divided into these subsets. Norepinephrine levels were available for 9 of the 12 Group A patients and showed a significant increase (532 ± 80 to 696 ± 73; $p < 0.02$). Epinephrine levels did not increase significantly in either subset.

Patient characteristics were examined for trends in each subset. There was no differentiation based on the presence of predominantly left ventricular failure versus biventricular failure or on the cause of CHF (ischemic versus nonischemic). All patient groups also had comparable degrees of excess edema.

Thus, the hemodynamic response to tilt in CHF was heterogeneous and could be divided into 3 patterns (Fig. 7). The hemodynamic variables of the 18 patients who had relatively intact peripheral pooling indicated less severe CHF compared to the 23 patients without pooling. Of the 18 patients who had pooling, 12 (Group A) had a reflex increase of systemic vascular resistance that was sufficient to prevent orthostatic hypotension despite the absence of reflex tachycardia or increase of plasma renin activity. Six patients (Group B) did not have reflex increases in resistance in response to venous pooling, and thus demonstrated marked orthostatic reduction of blood pressure. The largest group of patients (Group C, n = 23) which had more severe CHF, did not demonstrate afferent venous pooling, and thus did not have reflex efferent responses.

Discussion

In the normal response to gravitational stress of head-up tilt, the venous capacitance vessels accommodate an even larger proportion of the total blood volume causing both cardiac filling pressures and cardiac output to fall. Since cardiac output is a function of venous return, the reduction of cardiac index during tilt has been used as a measure of peripheral pooling. This venous pooling is difficult to quantify directly and may also depend on the ratio of cardiopulmonary blood volume to total blood volume.[11,15] In previous studies,[11,15] pooling was directly proportional to the reduction of cardiac output and is presumed to be present

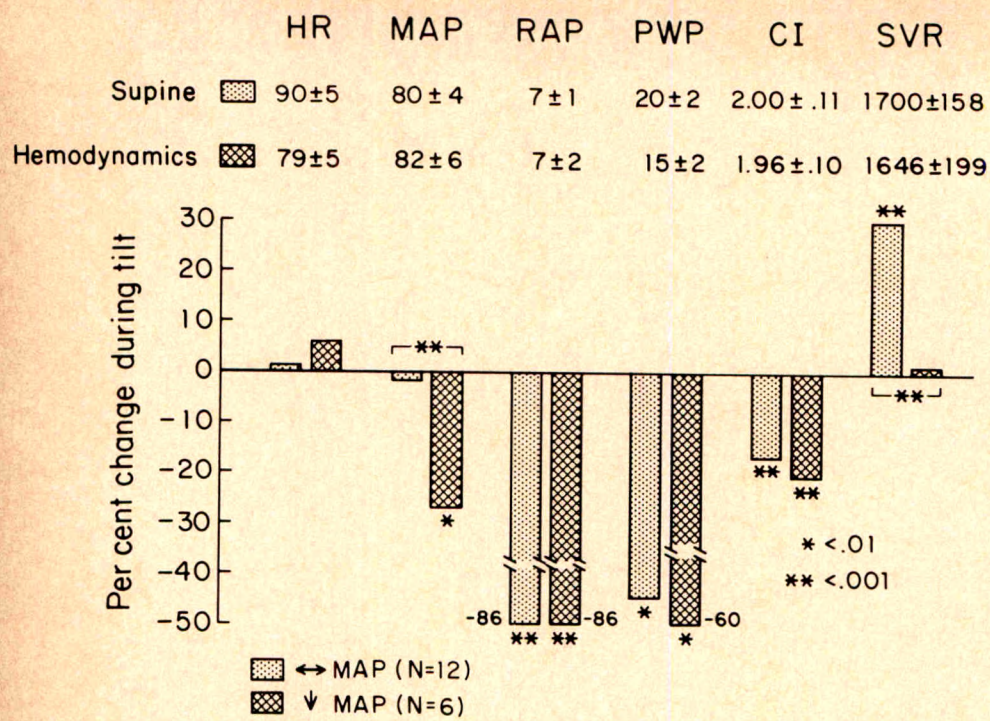

FIGURE 6. The 18 patients who demonstrated orthostatic reduction of cardiac index (CI) during tilt could be subdivided into patients who maintained blood pressure (↔MAP) (n = 12) and those who developed orthostatic hypotension (↓MAP) (n = 6)) during tilt. There was no significant difference of supine hemodynamics between the groups. Furthermore, during tilt, the magnitude of reduction of cardiac filling pressures and CI were comparable. However, the group of patients without orthostatic hypotension reflexly increase systemic vascular resistance (SVR), whereas those who developed orthostatic hypotension had an inadequate reflex increase of SVR, so that MAP fell. In neither group was there reflex tachycardia during tilt. HR = heart rate; RAP = right atrial pressure; PWP = pulmonary wedge pressure.

whenever cardiac output falls during tilt. When peripheral venous pooling and reduction of cardiac output activate atrial and low pressure mechanoreceptors, the neurohormonal efferent limb consists of decreased parasympathetic discharge, increased sympathetic discharge with an increase of circulating norepinephrine, and activation of the renin-angiotensin system.[7–10,16,17] The compensatory hemodynamic response is manifest by tachycardia and an increase in systemic resistance, which maintain blood pressure despite the 20 to 30% reduction of cardiac index.

In the present study of 41 CHF patients, the first major abnormality was the absence of tilt-induced peripheral pooling in 56% of the patients. Based on supine hemodyamics, the majority of patients (56%) with relatively intact pooling had lesser degrees of CHF. The extent of pooling was inversely correlated with supine pulmonary capillary wedge pressure, suggesting a continuum of autonomic dysfunction and hemodynamic reactivity in CHF. This continuum may be more apparent when the progression of CHF in a single patient is studied during extended follow-up.

The absence of afferent peripheral venous pooling in Group C patients is difficult to explain. It has been suggested that the ability to increase venous capacitance in the extremities of patients with chronic CHF is markedly reduced.[18,19] This reduction in capacitance is most likely secondary to generalized reflex venoconstriction, which may occur as a compensatory mechanism to increase cardiac output in the early stages of myocardial pump failure.[18] Other important factors include increased blood volume,[3] increased levels of circulating catecholamines,[4] and local extrinsic factors such as tissue edema, which decreases venous distensibility.[20] This last factor was recently identified as preventing venous pooling in patients with marked edema secondary to cirrhosis and the nephrotic syndrome.[21] Thus, in severe CHF, one might anticipate that the increase of venous capacitance during the stress of postural change would be markedly attenuated, and the afferent stimulus for activation of hemodynamic and neurohormonal pathways does not occur. This relatively fixed circulatory tone can be modified by vasoactive drugs, as demonstrated by the first dose administration of captopril.[4]

Group A patients (Fig. 7) had an increase in systemic resistance sufficient to maintain blood pressure. The magnitude of this increase was inversely correlated with the magnitude of cardiac output reduction. The increase in resistance was not accompanied by an increase of renin or circulating epinephrine. However, plasma norepinephrine levels, measured in 9 of these patients, did increase significantly, indicating some preservation of sympathetic responsiveness. Although these patients had better supine hemodynamic values than Group C, multiple clinical variables did not further characterize this group. Thus, some patients with less severe CHF respond to the afferent stimulus of pooling with many of the elements of the normal efferent response.

The 6 patients in Group B (Fig. 7) had marked abnormalities of the efferent response to head-up tilt, and experienced marked orthostasis. This response is analogous to patients with idiopathic orthostatic hypotension, although by standard clinical criteria, these patients did not have this problem or other common causes of orthostatic hypotension. This particular subset may not tolerate vasodilator therapy and may require alternate therapy with inotropic agents. Orthostatic hypotension in this group was not related to differences in baseline filling pressures.

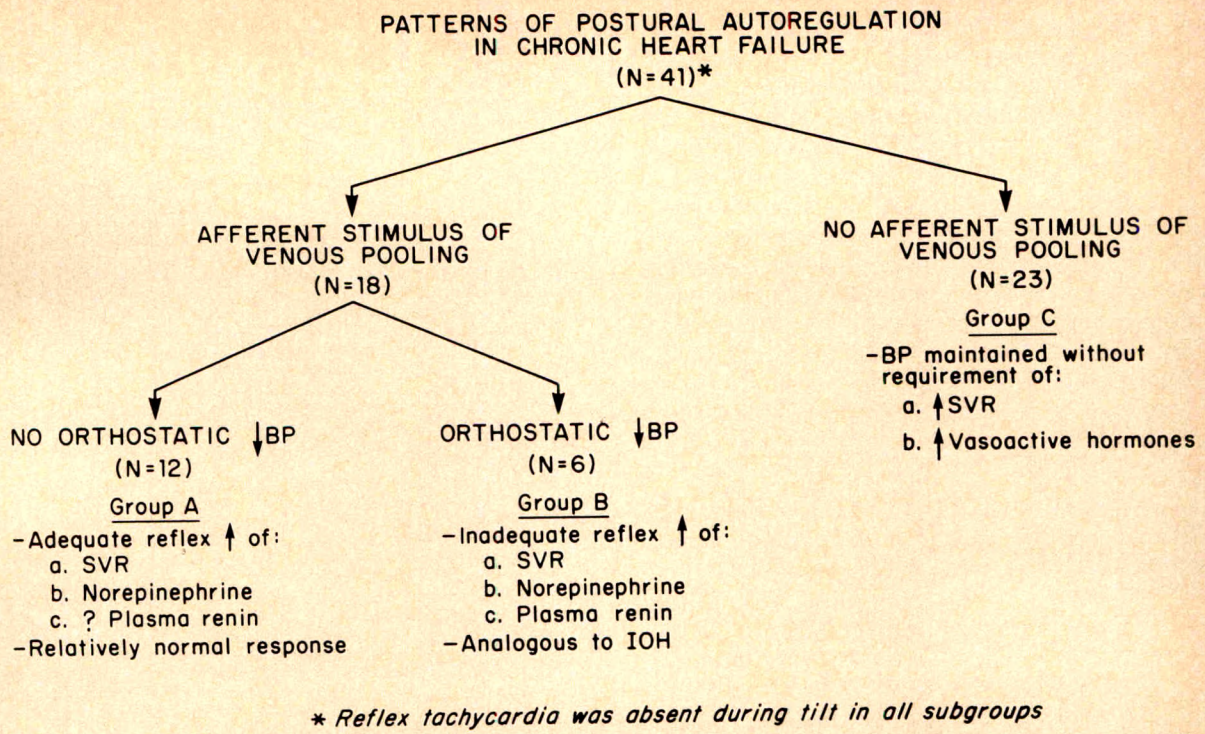

FIGURE 7. The hemodynamic and neurohormonal response of circulatory autoregulation in heart failure were divided into 3 groups. Patients who had the afferent stimulus of venous pooling were subdivided into those who had no orthostatic reduction of blood pressure (no orthostatic ↓BP) (Group A) owing to relatively normal autoregulation, and those who had significant orthostatic reduction of BP (Group B) owing to an inadequate hemodynamic and neurohormonal response to peripheral pooling. Group B patients are analogous to patients with idiopathic orthostatic hypotension (IOH). Group C patients had no afferent stimulus of venous pooling during head-up tilt. Therefore, there was no efferent response of hemodynamic and neurohormonal pathways. SVR = systemic vascular resistance.

The potential effect of diuretics on the different patterns of response must also be considered. All patients were receiving furosemide and, in many cases, a thiazide-like preparation. Unlike other disease entities,[21] diuretic therapy of patients with CHF may change supine hemodynamics but not the qualitative response to tilt,[22] because blood volume usually remains expanded. In a recent study,[23] there was no significant qualitative change in the tilt response of individual CHF patients, who were studied in balance during both sodium depletion (10 mEq) and sodium repletion (100 mEq). These patients also did not have a significant change in total blood volume as dietary sodium was altered. Thus, it is unlikely that variation in diuretic dosage has a major influence in differentiating these 3 patterns of hemodynamic response to tilt.

Heart rate remained relatively constant in all 3 patterns despite the wide range of hemodynamic changes during tilt. Abnormalities of heart rate responses due to changes in parasympathetic and sympathetic tone have been identified.[3,4,24,25] The present data further emphasize that the heart rate response to physiologic maneuvers and vasodilator therapy must be interpreted in light of underlying autonomic dysfunction.

The renin-angiotensin system is activated to a variable degree in CHF, as manifest by the wide range of baseline supine plasma renin activity.[26] Patients with relatively intact pooling had lower supine plasma renin activity overall, and retained some degree of renin responsiveness to tilt. For Group C patients, the lack of a tilt-induced increase of renin may represent blunted efferent responsiveness or inadequate stimulus of cardiopulmonary mechanoreceptors. In contrast to the latter abnormality, plasma renin activity can be changed by dietary sodium manipulation in CHF.[23] This suggests a dissociation of cardiopulmonary reflex and macula densa signals for renin release. In a recent study, with classification of patients by stress hormone levels, subgroups of renin responses during ambulation were identified.[27] However, ambulation, through muscular contraction in the lower limbs, results in venous compression with reversal of pooling,[28] so this renin response may be more analogous to exercise.

Despite similarities of supine norepinephrine levels in Groups A and C, only Group A retained the ability to reflexly increase norepinephrine. This preserved sympathetic responsiveness may be another useful guide to monitor the progression of CHF. Although sympathetic responsiveness is usually attenuated with severe CHF, this may be reversible. After hemodynamic improvement with long-term captopril therapy, norepinephrine responsiveness to tilt has been demonstrated.[29] Levine et al[30] demonstrated normalization of the norepinephrine response to tilt and exercise after successful heart transplantation.

The importance of understanding the response to head-up tilt in patients with heart failure is emphasized by several factors. First, the heterogeneity of the ab-

normalities seen in the present study may help to explain some of the discrepancies between supine and upright exercise.[31] Second, supine filling pressures appear to be important determinants of peripheral pooling, but there is no "critical" filling pressure for orthostasis in CHF. Third, physiologic maneuvers such as head-up tilt are necessary to clarify pathophysiologic mechanisms in CHF, given the paucity of applicable animal model data. Fourth, understanding the heterogeneity of response may aid in the choice of appropriate drug therapy and minimize side effects such as orthostatic hypotension. Finally, a better understanding of circulatory autoregulation may be necessary for the analysis of CHF in its progression from mild to more severe symptoms.

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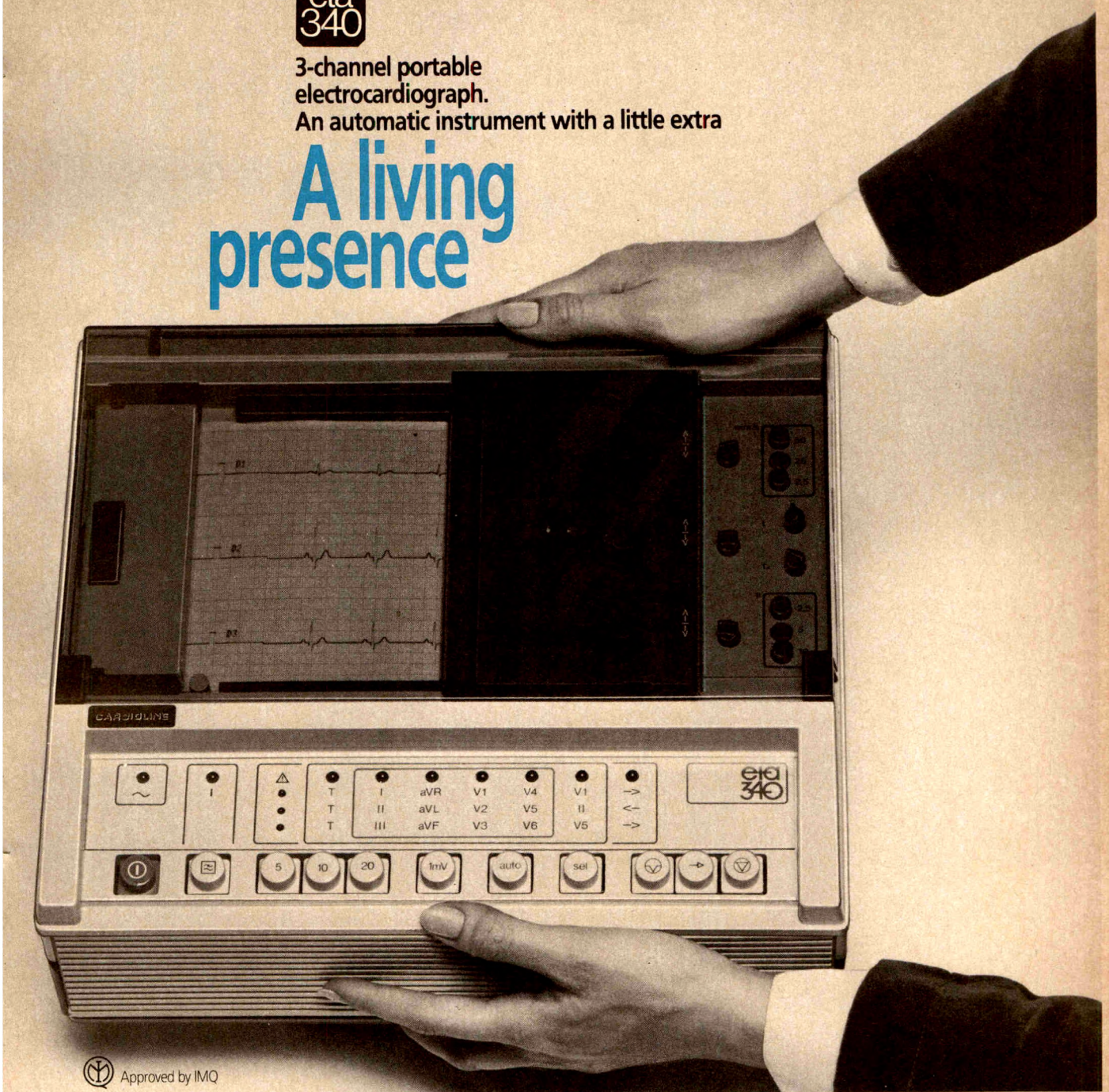

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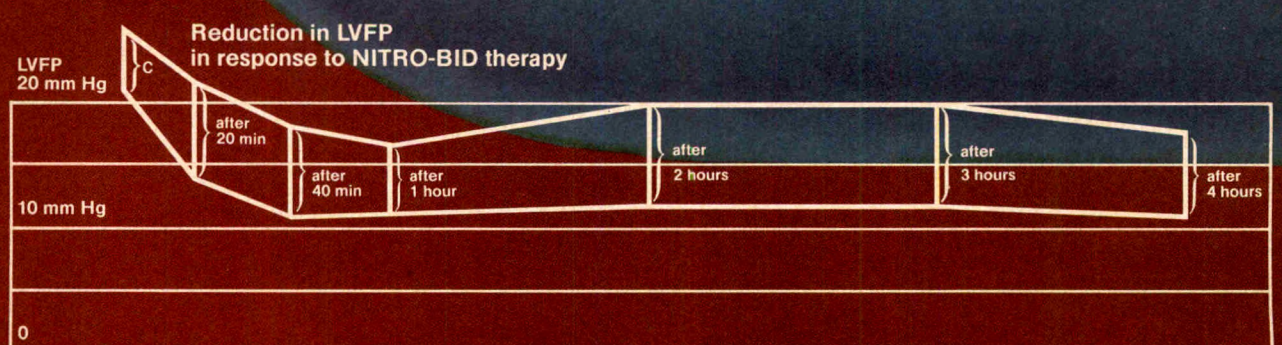

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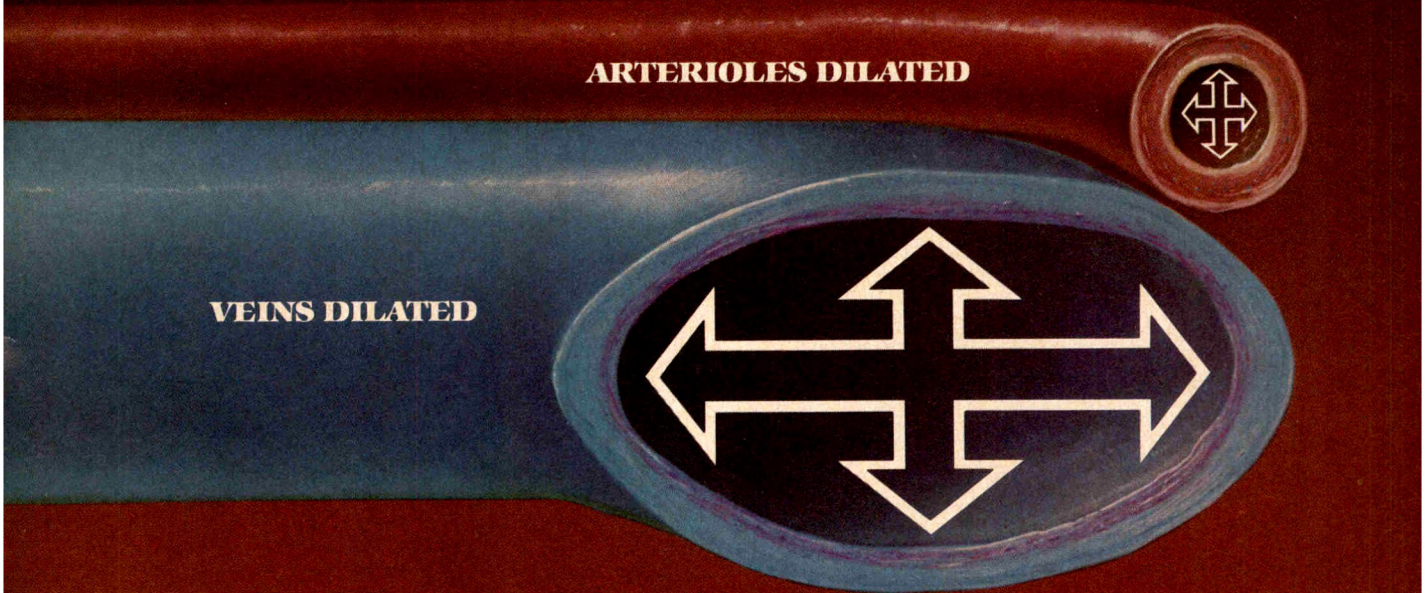

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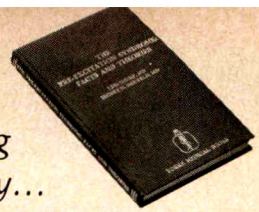

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

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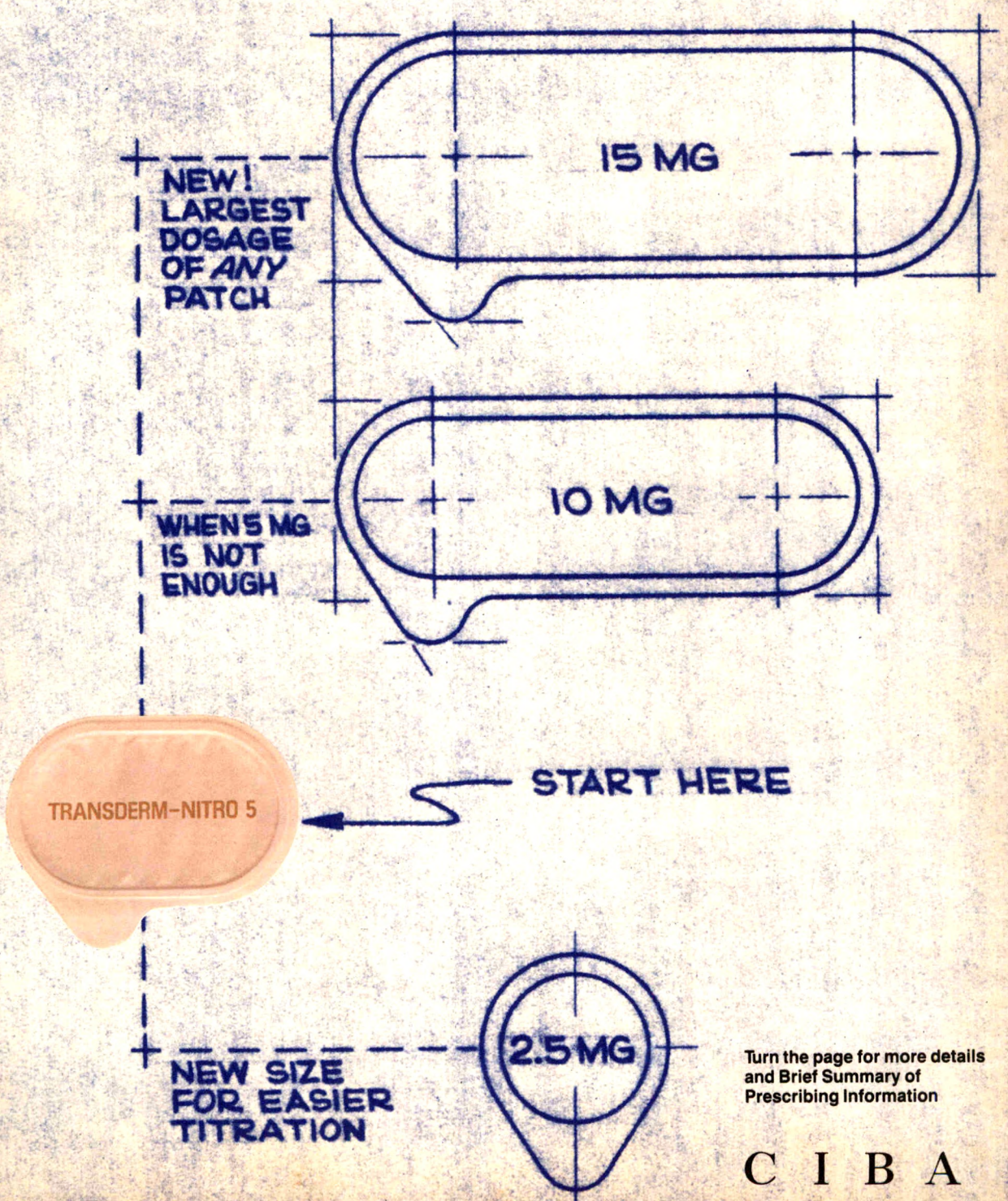

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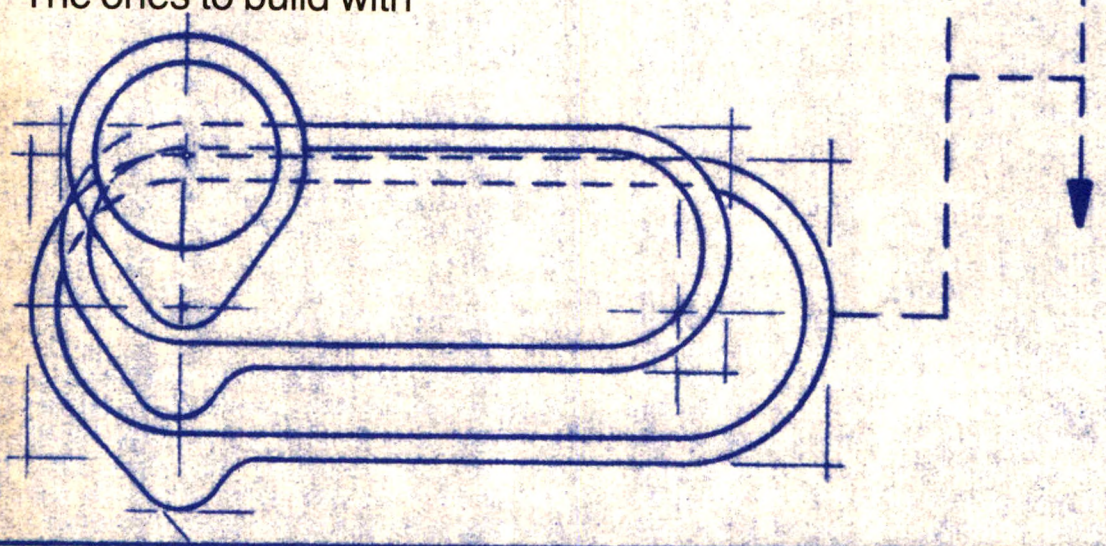

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Accuracy of Evaluation of the Presence and Severity of Aortic and Mitral Regurgitation by Contrast 2-Dimensional Echocardiography

CHERYL L. REID, MD, DAVID T. KAWANISHI, MD, CHARLES R. McKAY, MD, URI ELKAYAM, MD, SHAHBUDIN H. RAHIMTOOLA, MB, FRCP, and P. ANTHONY N. CHANDRARATNA, MD, MRCP

Contrast 2-dimensional (2-D) echocardiography was performed during cardiac catheterization to compare the technique with cineangiography in evaluating the presence and severity of aortic (AR) and mitral regurgitation (MR). A physiologic solution was injected through the intracardiac catheter while echocardiograms were recorded in multiple views.

AR was evaluated in 35 patients; an adequate 2-D echocardiogram was obtained in every patient. Cineangiography was adequate for diagnosis in every patient, but in 3 patients AR could not be graded because of technical problems. Twenty-six patients had AR by 2-D echocardiography and cineangiography and 9 did not have AR by either 2-D echocardiography or cineangiography. Thus, the specificity, sensitivity and predictive accuracy was 100% for detection of AR by 2-D echocardiography. Severity of AR was graded (0 to 4+) by visual inspection in both methods, and severity by both methods correlated with r = 0.998.

MR was evaluated in 59 patients. Because of technical problems, MR could not be evaluated by cineangiography in 15, by 2-D echocardiography in 5, or by either method in 2. In 2 patients, although it could be detected, the severity of MR could not be graded by cineangiography. Of 37 patients with satisfactory studies, MR was detected by 2-D echocardiography and by cineangiography in 16; MR was detected only by 2-D echocardiography in 2, only by cineangiography in 3 and by neither method in 16. The sensitivity of 2-D echocardiography for detection of MR was 84%, specificity 89%, positive predictive accuracy 89%, and negative predictive accuracy 84% compared with cineangiography. The severity of MR by both methods correlated with r = 0.998.

Contrast 2-D echocardiography for the evaluation of the presence and severity of AR and MR is both sensitive and specific, particularly for AR. In the cardiac catheterization laboratory, this method should be of greatest value when use of cineangiography is limited by the dose of contrast medium, radiation or by technical problems, particularly those encountered with left ventricular angiography.

(Am J Cardiol 1983;52:519–524)

Contrast echocardiography is a technique that consists of injecting a previously agitated solution through a peripheral vein or intracardiac catheter while echocardiographic recordings are obtained. The contrast effect is a result of microbubbles produced in the solution by the previous agitation and which, although not grossly visible, are detectable by ultrasound.[1] A variety of solutions can cause the contrast effect; the most frequently used are saline solution or dextrose in water, indocyanine green dye, or the patient's blood.[2,3] The method has been used to assess flow patterns in congenital heart disease, to detect intracardiac shunts, and to evaluate the presence of tricuspid insufficiency.[4–6] Contrast M-mode echocardiography has been used during cardiac catheterization to detect aortic (AR) and mitral regurgitation (MR).[7] The severity of the regurgitant lesions, however, cannot be adequately assessed by M-mode echocardiography because of the limited

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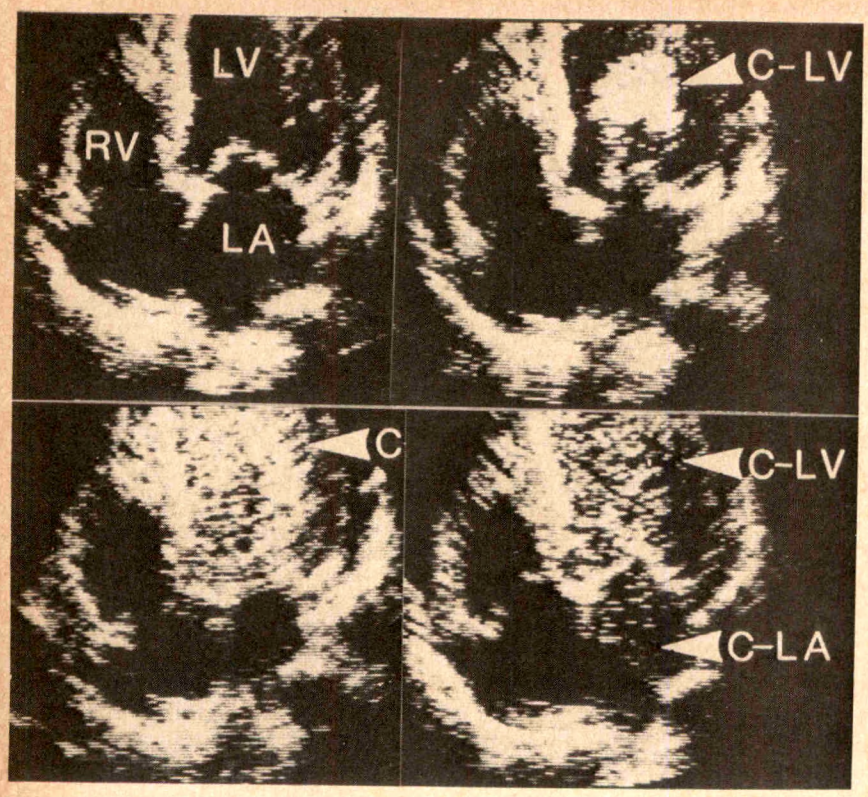

FIGURE 1. Top left, before contrast injection, a 2-dimensional (2-D) echocardiogram in the apical 4-chamber view of a patient with aortic regurgitation. The intracardiac catheter positioned in the aortic root is not visualized in this view. **Top right,** a cloud of microbubbles appears in the left ventricle (LV) immediately after injection of contrast C-LV). **Bottom left,** the microbubbles densely fill the entire left ventricular chamber by the end of the first diastolic interval after the injection. The severity of the aortic regurgitation was graded as 4+ by both 2-D echocardiography and cineangiography. **Bottom right,** a few microbubbles were visualized in the left atrium (C-LA) during systole and was graded as 1+ mitral regurgitation. The mitral regurgitation was graded as 1+ by cineangiography after review by the third angiographer. RV = right ventricle.

view of the intracardiac chambers. Two-dimensional (2-D) echocardiography is particularly useful because of the added spatial orientation that it provides. Therefore, this study compared the accuracy of contrast 2-D echocardiography with a standard semiquantitative cineangiographic method during cardiac catheterization in the assessment of the diagnosis and severity of AR and MR.

Methods

Patients: Sixty patients who underwent diagnostic cardiac catheterization were studied. All contrast 2-D echocardiographic studies were performed by 2 of the investigators; patient selection was based only on the availability of the personnel and the echocardiographic equipment. No patient was excluded because of precatheterization echocardiographic findings. There were 38 males and 22 females, mean age 49 years (range 16 to 75). Thirty-one of the patients had coronary artery disease, 12 rheumatic valvular disease, 5 AR of uncertain cause, 4 infective endocarditis, 2 mitral valve prolapse syndrome, 1 prosthetic valve dysfunction, 2 chest pain with normal coronary arteries, 1 a left atrial myxoma and 2 thoracic trauma. One patient had undergone a second study after prosthetic valve replacement with a Starr-Edwards valve for rheumatic heart disease. Thirty-three patients had undergone both aortic root and left ventricular angiography.

Cardiac catheterization and angiography: Left- and right-sided cardiac catheterizations were performed using the retrograde femoral technique. After measuring left- and right-sided cardiac pressures and cardiac output, left ventricular contrast angiography was performed in the right and left anterior oblique positions. When clinically indicated, supravalvular cineaortography was performed in the left anterior oblique position. AR was graded semiquantitatively from the supravalvular aortogram according to a previously described method[8]: 1+ (mild), contrast material clears with each beat and never fills the left ventricle; 2+ (moderate), faint opacification with the contrast material of the entire chamber; 3+ (moderately severe), opacification of the left ventricle with an intensity equal to the aorta; and 4+ (severe), complete opacification of the left ventricle with the first beat and with appearance of progressively greater intensity than the aorta. MR was graded semiquantitatively from the left ventriculogram as follows[9]: 1+ (mild), the contrast material clears with each beat and never opacifies the left atrium; 2+ (moderate), the contrast material does not clear with 1 beat and opacifies the left atrium after several beats; 3+ (moderately severe), the left atrium opacifies with contrast material to an intensity equal to that of the left ventricle; and 4+ (severe), the left atrium opacifies within 1 beat and becomes progressively more dense with each beat. Premature beats during the left ventriculogram were excluded in the evaluation of MR. Cineangiograms in which the regurgitant chamber was inadequately visualized for grading purposes were included only for detection of the presence of regurgitation. Each cineangiogram was evaluated independently by 2 experienced angiographers for the presence and severity of the regurgitation. The reviewers were blinded at the time of evaluation to each other and to the identity of the patient. When there was a disagreement, a consensus was reached. If that was not possible, a third experienced observer was used for the final interpretation.

Contrast 2-D echocardiography: Two-dimensional echocardiography was performed using an ATL (Advanced Technology Laboratory, Inc.) real-time mechanical sector scanner with a simultaneous electrocardiogram. The images were recorded on a Sanyo videotape system. These recordings were then transferred to a Diasonics Cardio-Revue Center to facilitate playback analysis using a videodisc. The contrast effect was produced by vigorously shaking a 10-ml syringe that contained a dilute standard cardiac catheterization flush solution consisting of 2.5% dextrose in water with 2 U/ml of

heparin. In a limited trial, we found that this solution produced adequate contrast and was then chosen as the contrast agent primarily because it was convenient. After carefully clearing visible bubbles, the solution was rapidly hand-injected through the intracardiac catheter while echocardiographic recordings were made beginning a few beats before the injection and continuing until the microbubbles disappeared. Voice recordings were made on the videotape to describe the catheter position and note the time of the injection. Recordings were made in the supine or left lateral position. Care was taken to avoid movement of the catheter between the echocardiographic and cineangiographic studies.

Contrast 2-D echocardiographic studies with injection into the aortic root were usually performed before supravalvular aortography when the latter procedure was indicated. The parasternal long-axis view was examined first and adjustments were made to obtain the clearest view of the left ventricle and aortic root. Gain settings were adjusted to reduce the level of background noise. The injection was then repeated in other views, including the apical 4-chamber, apical 2-chamber or subcostal position to confirm the findings. AR was considered to be absent if no microbubbles were visualized in the left ventricle in at least 2 views, and, when adequately visualized, a good contrast effect was seen in the aortic root. A study for AR was considered positive when microbubbles were seen in the left ventricle in any echocardiographic view (Fig. 1).

Injections into the left ventricle for detection of MR were made after hemodynamic recordings were obtained and before injection of angiographic contrast media. In 1 patient with coronary artery disease, the angiographic study was performed first, after which the patient developed chest pain, became dyspneic, and the left ventricular pressure was seen to increase. No MR was seen on the angiogram. The contrast 2-D echocardiographic study was then performed and MR was present. The different findings by the 2 techniques could have been explained by the development of left ventricular dysfunction[10] and acute transient MR after left ventricular angiography. Because of this possibility, all contrast echocardiographic studies were subsequently performed before angiographic studies. Echocardiographic views were done in the positions that gave the clearest image of the left atrium with adjustments made to reduce background noise. MR was considered present if microbubbles were seen in the left atrium in any view (Fig. 1) and negative if no contrast effect was seen in the left atrium in at least 2 views. If a premature ventricular contraction occurred during the left ventricular injection, the injection was repeated. In many patients a slightly "off-axis" view was used to obtain the clearest image of the regurgitant chamber. Multiple injections were often necessary to assure adequate recordings and visualization of microbubbles.

AR was semiquantitatively graded by echocardiography as follows: 1+ (mild), only a few microbubbles appear in the left ventricular outflow tract and never reach a density sufficient to outline the left ventricle; 2+ (moderate), the left ventricle is sparsely outlined with the microbubbles, but clears within a few beats; 3+ (moderately severe), the left ventricle is densely filled and, when the aortic root is also visualized, they are of equal density; and 4+ (severe), the left ventricle is densely filled within the first beat and the microbubbles persist for several beats. The severity of the MR assessed by contrast echocardiography was graded as follows: 1+ (mild), appearance of only a few microbubbles of insufficient quantity to outline the left atrium; 2+ (moderate), the left atrium is outlined with the microbubbles after several beats but less densely than the left ventricle; 3+ (moderately severe), the atrium completely fills with microbubbles to a density equal to the left ventricle; and 4+ (severe), the left atrium is filled with microbubbles to a progressively greater density than the left ventricle with each beat. MR associated with premature ventricular contractions was excluded. Each 2-D echocardiographic study was evaluated independently by 2 experienced echocardiographers who were also blinded to the results of the angiography and the identity of the patient. When there was disagreement as to the presence or severity of the regurgitation, a consensus was taken as the final interpretation.

The patients were all observed in the hospital for 24 hours after cardiac catheterization. No neurologic symptoms or complications were noted.

Data analysis: Cineangiograms with excessive premature ventricular contractions or of inadequate technical quality for detection of valvular regurgitation were seen in 17 patients (28%) and were excluded from analysis. In 7 patients (11%), echocardiograms were of inadequate technical quality for analysis. McNemar's chi-square analyses were performed to evaluate the sensitivity of the 2-D echocardiographic technique. Spearman's rank correlation coefficients were calculated to compare the agreement between the semiquantitative method of the 2 techniques.[11] Spearman's rank correlation was used because the variables in this case are discrete and not continuous and, therefore, the usual Pearson correlation is not appropriate. Because the variables are discrete, their correlations tend to be exaggerated compared with those for continuous data. However, the strength of the correlation is not artifactually affected by the statistical calculation. Sensitivity was defined as true positives/true positives + false negatives. Specificity was defined as true negatives/true negatives + false positives. Predictive value of a positive test was defined as true positives/all positives (true positives + false positives); predictive value of a negative test was defined as true negatives/all negatives (true negatives + false negatives).

Results

Aortic regurgitation: AR was evaluated in 35 patients; technically adequate contrast 2-D echocardiograms were obtained in all. Cineangiography was adequate for diagnosis in all, but in 3 patients severity could not be graded.

Twenty-six of the 35 patients had AR by both contrast 2-D echocardiography and cineangiography. Nine patients had no AR by either contrast 2-D echocardiography or cineangiography, yielding a sensitivity, specificity and predictive value of 100% for detection of AR by contrast 2-D echocardiography (Table I) compared with that for cineangiography. Therefore, for detection of AR, there was perfect agreement between the techniques (chi-square = 0, difference not significant [NS]).*

In 20 patients there was exact agreement between 2-D echocardiography and cineangiography in the visual assessment of the severity of the AR. In 12 patients, although the 2 techniques differed, it was not by >1 grading scale (Fig. 2). The Spearman correlation coefficient measuring the degree of association between both techniques was $r = 0.998$ ($p < 0.0001$).

Mitral regurgitation: MR was evaluated in 59 patients. Technical problems prevented the evaluation of MR by cineangiography in 15, by 2-D echocardiography in 5, and by either method in 2. In 2 patients, the severity of MR could not be assessed by cineangiography.

* To calculate McNemar's chi-square analysis, it was necessary to add 0.5 to each cell.

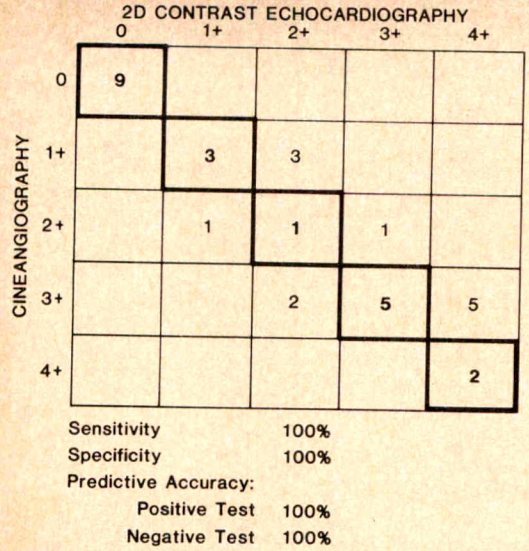

FIGURE 2. The semiquantitative assessment by contrast 2-dimensional (2D) echocardiography and cineangiography of aortic regurgitation.

Of 37 patients with satisfactory studies, results of contrast 2-D echocardiography and cineangiography were both positive in 16. MR was detected only by cineangiography in 3; only by 2-D echocardiography in 2; and by neither technique in 16 patients (chi-square = 0.2, NS). One of the patients with MR detected only by 2-D echocardiography was the patient who had cineangiography first and then developed severe chest pain and possibly acute MR. The other patient was graded 1+ by 2-D echocardiography. The 3 patients who did not appear to have MR by contrast echocardiography all had only 1+ MR by cineangiography. Compared with cineangiography, contrast 2-D echocardiography for detection of MR had a sensitivity of 84%, a specificity of 89%, a predictive value for the presence of MR of 89%, and an 84% predictive value for its absence (Table I).

The association between both techniques for assessment of the severity of the MR measured by Spearman's rank correlation coefficient was r = 0.998 ($p < 0.0001$). Twenty-five of the patients had equal severity of MR assessed by both 2-D echocardiography and cineangiography; in 8 patients there was a difference of 1 grade between both techniques, and in 1 patient a difference of 2 grades (Fig. 3).

Discussion

Our results showed that contrast 2-D echocardiography during cardiac catheterization was highly sensitive and specific in the detection of left-sided valvular regurgitation compared with cineangiography. The semiquantitative assessment of the severity of the regurgitation based on a visual grading scale had an excellent correlation with that obtained by cineangiography. The technique was safe provided care was taken to remove visible bubbles before injection; no complications were noted with this method during the study.

Cardiac catheterization with angiography has been the standard method for assessment of the presence and

TABLE I Detection of Aortic Regurgitation (AR) and Mitral Regurgitation (MR) by Contrast 2-Dimensional Echocardiography

	2-D Echocardiography			
	AR		MR	
Angiography	0	+	0	+
0	9	0	16	2
+	0	26	3	16

0 = negative test; + = positive test.

severity of valvular regurgitation. Although the semiquantitative assessment by cineangiography has limitations and a discrepancy between it and direct measurement of the amount of valvular regurgitation has been shown, it remains a widely used method.[12] However, it has the following disadvantages: (1) the use of contrast media; (2) a limited number of angiographic views can be obtained (because of the maximal dose of contrast dye that can be used in an individual patient); (3) exposure to radiation; and (4) technical problems such as malpositioning of the intracardiac catheter and patient or premature ventricular contractions that may occur during the angiogram. The latter is a problem particularly with left ventriculography and may prevent accurate evaluation of left ventricular function and the detection and quantitation of MR.

Although contrast 2-D echocardiography does not obviate the need for cardiac catheterization, it could be a useful adjunct to this procedure in situations in which the use of standard contrast cineangiography would be limited for some of the reasons noted previously. For example, we successfully used this method in a patient with severe heart failure who had suspected malfunction of prosthetic mitral and aortic valves in whom the physician caring for the patient believed that the use of contrast dye with its hemodynamic effects might be hazardous. Contrast media used in angiography causes peripheral vasodilatation, increased intravascular volume and increased cardiac output.[13] In patients whose left ventricular function is already compromised because of ischemic or valvular heart disease, these physiologic alterations may pose a significant clinical problem.[13] In addition, contrast-induced renal failure may be precipitated, particularly in patients with preexisting renal disease.[14] Finally, severe allergic reactions, although uncommon, may occur.[15] Thus, the use of contrast dye may not be desirable in some selected patients.

Another advantage of this technique is that multiple injections may be performed in different 2-D echocardiographic views to assess complex intracardiac flow patterns.[16] Cineangiography in these situations is limited by the dosage of contrast medium that may be used in an individual patient and by the overlapping of contrast-filled structures. The ability to repeat a large number of injections with contrast 2-D echocardiography also facilitates the assessment of MR when there are frequent premature ventricular contractions that may occur with injection of contrast media during left ventricular cineangiography. By comparison, spurious

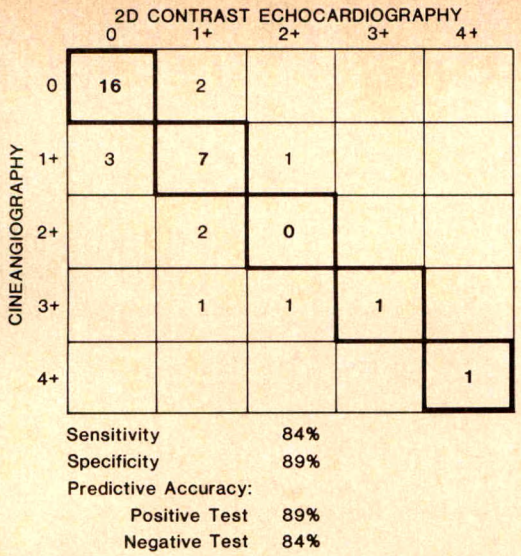

FIGURE 3. The semiquantitative assessment by contrast 2-dimensional (2D) echocardiography and cineangiography of mitral regurgitation.

MR due to premature ventricular contractions occurring spontaneously or, rarely, induced by the injection and irritation of the myocardium during contrast echocardiography is easily diagnosed; the injection is simply repeated after the contrast has cleared. (Once microbubbles appear in the left atrium it is difficult to assess further regurgitation during subsequent sinus beats until the chamber is again free of microbubbles.)

Finally, exposure to radiation can occassionally become a significant limitation to cineangiographic study as, for example, in pregnant patients, when adverse effects of the radiation to the fetus must be considered.[17,18] Contrast 3-D echocardiography during cardiac catheterization can be used to assess valvular lesions with minimal radiation exposure. Complete cardiac catheterization with hemodynamic data can thus be obtained that would facilitate appropriate management decisions during pregnancy.[18]

However, there are technical problems associated with 2-D echocardiography. The major problem is the inability to obtain adequate 2-D echocardiograms in all patients. We had an 11% incidence of inadequate studies from procedures performed during cardiac catheterization. A technically difficult study in the electrocardiographic laboratory before cardiac catheterization does not, however, necessarily preclude an adequate contrast study for valvular regurgitation. Multiple views may be used, including apical and subcostal views, to allow adequate visualization of the microbubbles. Often, a slightly "off-axis" view, which is inadequate for standard measurements or analysis, may still be used satisfactorily to visualize the regurgitant chamber being analyzed for microbubbles.

There are many causes of false-positive and false-negative studies with contrast 2-D echocardiography. The major problem is the presence of a high level of background noise that either prevents the detection of the microbubbles or may simulate their appearance. Often, microbubbles can be detected against a high level of background noise because of the characteristic movement pattern of the microbubbles. In 5 of our patients in whom 2-D echocardiography was incorrect in the detection of MR, the background noise was high and, in retrospect, 2 of these studies incorrectly read as negative had a few microbubbles seen in the left atrium. The 2 patients who had positive tests for MR by 2-D echocardiography that were negative by cineangiography were, in review, again read as positive; 1 patient, as mentioned previously, may have had acute, transient MR. However, it is also possible that the cineangiogram was not optimally positioned to detect a small amount of MR. Another cause of false-positive MR may be that which is induced by the catheter, and is therefore inconstant. False-negative studies by 2-D echocardiography might also be caused by a streaming or jet effect of the regurgitant lesion; therefore, we required that a negative visualization be present in at least 2 views in order to reduce this possibility. An inadequate injection of contrast would prevent adequate visualization of a contrast effect; therefore, it is important to be able to visualize the microbubbles at the site of injection. However, with aortic root injections, this was not possible in all patients; but in our study, we had no false-negative studies for AR. Improper placement of the catheter high in the aortic root may cause false-negatives for AR by either 2-D echocardiography or cineangiography and care should be taken to position the catheter properly. Five of the 7 studies graded as 4+ by 2-D echocardiography were graded 3+ by cineangiography. This discrepancy may reflect the tomographic nature of 2-D echocardiography. By sampling through a regurgitant jet (Fig. 1), the contrast may be detected at its earliest appearance, which is the major difference in the 2 grades. With cineangiography, the contrast may be diluted into a dilated left ventricle and, therefore, its detection delayed.

Visual assessment of the presence and severity of regurgitation is more difficult for MR than for AR, particularly if the left atrium is small and the regurgitation is mild. In our series, the difference in the severity of MR by the 2 techniques was >1 grade in only 1 patient. In AR, the correlation for grading of severity between contrast 2-D echocardiography and cineangiography was excellent ($r = 0.998$) and in no instance was the difference in grade >1. The visual grading scale that we devised for contrast echocardiography in the assessment of AR and MR is similar to the widely used grading assessment by contrast cineangiography and may, therefore, be easily adopted for this use.

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Two-Dimensional Echocardiographic Determination of Right Atrial Emptying Volume: A Noninvasive Index in Quantifying the Degree of Tricuspid Regurgitation

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Contrast echocardiography and inferior vena cava ultrasonography are useful techniques in diagnosing tricuspid regurgitation (TR) but are not helpful in estimating the severity. Using a computerized light-pen method for tracing the right atrial (RA) border during systole and diastole in the apical 4-chamber view, single-plane volume determinations were calculated in 10 normal subjects (Group I), 18 patients with atrial fibrillation (AF) and no TR (Group II), 14 patients with mitral stenosis and mild TR (Group IIIa), and 8 patients with mitral stenosis and severe TR (Group IIIb). TR was quantitated as absent, mild or severe by contrast right ventriculography. The RA end-systolic volume was 36.4 ± 13.1 ml in Group I patients, 59.1 ± 16.8 ml in Group II patients, 76.9 ± 55.4 ml in Group IIIa patients, and 154.6 ± 57.3 ml in Group IIIb patients (all Groups versus Group I, $p < 0.001$). The mean RA emptying volume, which equals RA end-systolic volume − RA end-diastolic volume, was 15.3 ± 5.0 for Group I, 17.7 ± 3.0 for Group II, 30.4 ± 8.0 for Group IIIa, and 71.6 ± 25.4 for Group IIIb. All 8 patients with severe TR but none of the 14 patients with mild TR had an RA emptying volume >40 ml ($p < 0.001$). In addition, all 28 patients in Groups I and II but only 4 of 14 patients in Group III had an RA emptying volume <26 ml ($p < 0.01$). The mean RA pressure measured at cardiac catheterization correlated with RA emptying volume ($r = 0.71$, $p < 0.001$). Thus, RA emptying volume is useful for separating severe TR from mild TR in patients with mitral stenosis.

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The clinical determination of the severity of tricuspid regurgitation (TR) at the bedside is often difficult. In TR, M-mode and 2-dimensional (2-D) echocardiography produce a nonspecific pattern of right ventricular volume overload.[1,2] Using peripheral contrast injections of saline solution, blood or indocyanine green, microcavitations or bubbles can be seen moving back and forth from the right atrium into the inferior vena cava.[3] Although M-mode and 2-D echocardiography are valuable in diagnosing TR, its severity is usually not determined. Recently, real-time inferior vena cava ultrasonography was found useful in distinguishing patients with severe TR from those with normal or mild TR in 75% of subjects.[4] Although exaggerated left atrial expansion during ventricular systole has been described in patients with severe mitral regurgitation (MR),[5] right atrial (RA) expansion in patients with TR has not been studied. This report evaluated RA emptying volume in quantifying the degree of TR in patients with mitral stenosis.

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Methods

Patients: The 2-D echocardiographic data in 50 patients form the basis of this report. The control group consisted of 10 consecutive patients; all had normal sinus rhythm with normal hemodynamic values, left ventriculography and coronary angiography at cardiac catheterization (Group I). Eighteen patients with atrial fibrillation (AF) without evidence of TR constituted Group II. Thirteen patients had coronary or hypertensive cardiovascular disease and 2 had dilated cardiomyopathy without valvular involvement. Three of the 18 patients had mitral stenosis without TR as determined by right ventriculography. Group III included 22 patients with pure rheumatic mitral stenosis (without MR); all had TR by contrast right ventriculography. All patients underwent complete left- and right-sided cardiac catheterization. The mitral valve area was calculated using the Gorlin formula.[6]

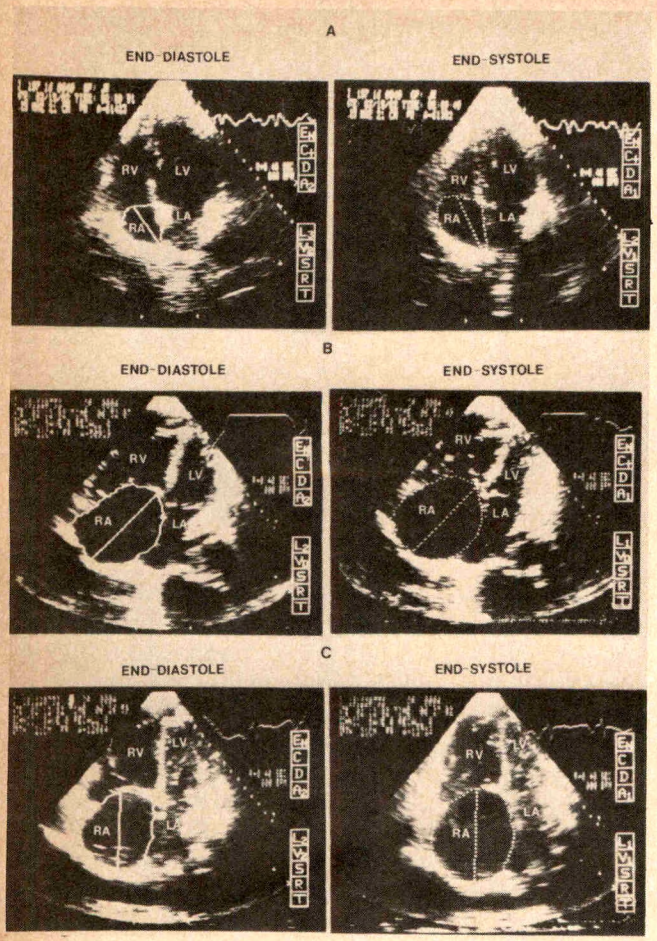

FIGURE 1. A, computerized light-pen method for tracing the right atrial (RA) border in the 4-chambered apical view in end-diastolic and end-systole in a normal control subject (Group I). The RA emptying volume is 14 ml. **B,** RA endocardial tracing in a patient with mild tricuspid regurgitation (Group IIIa). The RA emptying volume is 38 ml. **C,** RA endocardial tracing in a patient with severe tricuspid regurgitation (Group IIIb). The RA emptying volume is 80 ml. LA = left atrium; LV = left ventricle; RV = right ventricle.

Contrast right ventricular angiography was performed percutaneously by way of the transfemoral route with the patient in the right anterior oblique projection. TR was quantitated as absent, mild and moderate-severe (or significant). In mild TR, contrast material refluxed from the right ventricle into the right atrium at a point other than where the catheter crossed the tricuspid valve. In addition, the amount of contrast material refluxed was not enough to fully opacify the right atrium or any part of the vena cava. (TR only at the point where the catheter crossed the tricuspid valve was considered artifactual.) In moderate-severe TR, the right atrium was completely opacified or the venae cavae were partially opacified, or both.

Echocardiography: All patients were examined within 24 hours of cardiac catheterization by real-time cross-sectional echocardiography using a Varian V-3400 or V-3400 R phased-array sector scanner with a 2.25-MHz transducer. Echocardiograms were taken at 60 frames/s and recorded on videotape. Single images were photographed with a mounted Polaroid® camera. An electrocardiogram was recorded and displayed simultaneously to allow for timing of intracardiac events.

The right atrium was evaluated in the 4-chamber apical view. In all patients the ultrasonic transducer was positioned at the point of the maximal cardiac impulse and angled toward the right shoulder until an image was obtained that included all 4 cardiac chambers and both the mitral and tricuspid valves. Thereafter, the transducer was angled to obtain the maximal RA and right ventricular size while recording portions of both atrioventricular valves.[7] The modified 4-chamber view was chosen because it most clearly defines the RA border. In addition, dynamic RA motion can be evaluated in this view.

A computerized light-pen method for tracing the RA border was used. End-diastole was taken as the smallest RA dimension and end-systole as the largest atrial dimension (Fig. 1). Single-plane volume determination was made for both end-diastole and end-systole using the area-length method. The formula calculated for volume (V) is $8A^2/3$ L, where A = area and L = length.[8,9] We defined the emptying (or expansion) volume (RAEV) as end-systolic RA volume (ESV) − end-diastolic RA volume.

Expansion rate represented a measure of the rate of RA filling and was defined as expansion volume/expansion time. Expansion time represents the time from the onset of the QRS complex to the end of the T wave in seconds. RA ejection fraction was calculated as expansion volume/end-systolic volume.

All measurements were made during quiet respiration. In patients with AF, 4 consecutive representative cycles were analyzed and averaged. The cause of TR was considered organic if a thickened valve with restricted motion was noted on 2-D echocardiography. Normal-appearing tricuspid valve motion with good excursion of the individual leaflets indicated functional TR secondary to pulmonary hypertension. Echocardiographic measurements of RA volumes were performed independently in a blinded fashion without the knowledge of the angiographic findings. Intraobserver variation for 2-D echocardiographic RA volume determinations was 5.3%.

Statistical analysis: Statistical analysis was performed using the chi-square method, *t* test and analysis of variance and linear regression analysis when appropriate. The following definitions of statistical terms were used:

$$\text{Sensitivity} = \frac{\text{True positive (TP)}}{\text{true positive + false negative (FN)}} \times 100$$

$$\text{Specificity} = \frac{\text{True negative (TN)}}{\text{True negative + false positive (FP)}} \times 100$$

$$\text{Positive predictive value} = \frac{TP}{TP + FP} \times 100$$

$$\text{Negative predictive value} = \frac{TN}{TN + FN} \times 100$$

$$\text{Predictive accuracy} = \frac{TP + TN}{TN + FN + TP + FP} \times 100$$

Results

Study group: The 10 Group I patients consisted of 6 women and 4 men, aged 23 to 65 years. The 18 Group II patients consisted of 12 men and 6 women, aged 41 to 87 years. The 22 Group III patients consisted of 4 men and 18 women, aged 34 to 71 years. Nineteen Group III patients had AF and 3 were in sinus rhythm. Group III was subdivided into Group IIIa, which included 14 patients with angiographic mild TR, and Group IIIb, which included 8 patients with severe TR. Although the mitral valve area was smaller in Group IIIb than in Group IIIa patients, this difference was not significant (NS) (0.84 ± 0.34 cm^2 versus 1.17 ± 0.68 cm^2). The heart rate ranged from 54 to 98 beats/min.

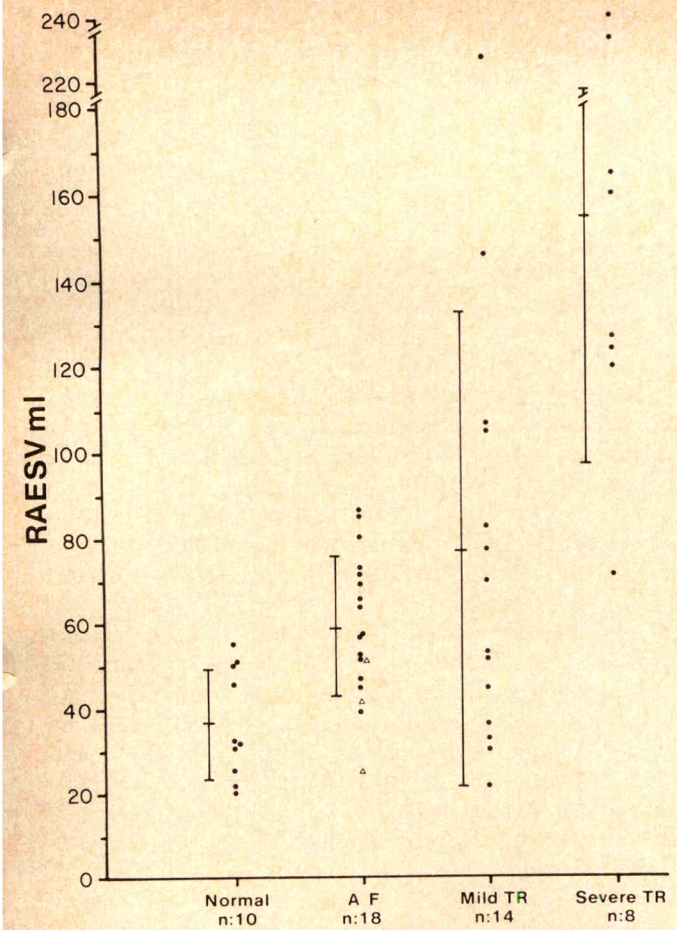

FIGURE 2. Right atrial end-systolic volume (RAESV) for the 4 groups of patients. **Bars** indicate the mean ± standard deviation. **Open triangles** indicate patients with mitral stenosis and no tricuspid regurgitation (TR) on right ventriculography. AF = atrial fibrillation.

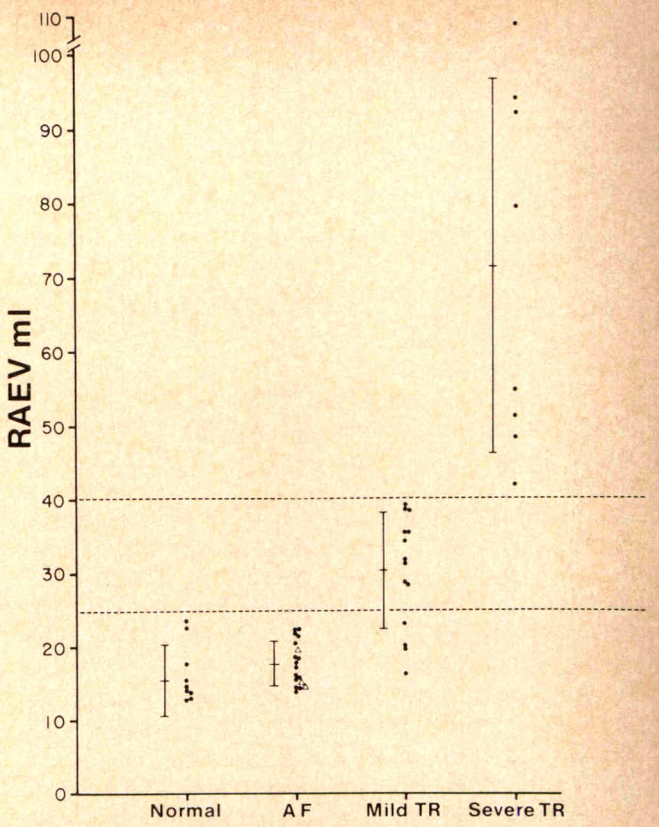

FIGURE 3. Right atrial emptying volume (RAEV) for the 4 groups of patients. **Open triangles** indicate patients with mitral stenosis and no tricuspid regurgitation (TR) on right ventriculography. AF = atrial fibrillation.

Right atrial volume dimensions: The mean RA end-systolic volume was similar for the 10 control patients with normal sinus rhythm (Group I) and the 18 patients with AF (Group II), but was significantly larger for the 22 patients with TR (Group III). The mean RA end-systolic volume was significantly larger in patients with severe TR (Group IIIb) than in those with mild TR (Group IIIa) ($p < 0.01$) (Fig. 2). Although the RA end-diastolic volume was larger in patients in Group IIIb than in patients in Group IIIa, this difference was not significant (82.9 ± 54 versus 47.4 ± 52 ml).

Right atrial phasic changes: The RA emptying volume was 15.3 ± 5.0 ml in Group I patients, 17.7 ± 3.0 ml in Group II patients and 45.4 ± 25.8 ml in the Group III patients. The RA emptying volume further separated patients in Group IIIa (mild TR) from those in Group IIIb (severe TR) (Fig 3). All 8 patients in Group IIIb had an RA emptying volume >40 ml, compared with none of the 42 patients in Group I, II or IIIa ($p < 0.001$). All Group I and II patients had an RA emptying volume <26 ml, whereas 10 of 14 Group IIIa patients had an RA emptying volume >26 ml ($p < 0.01$). Patients in Group II had a lower RA ejection fraction than patients in the other groups (Table I).

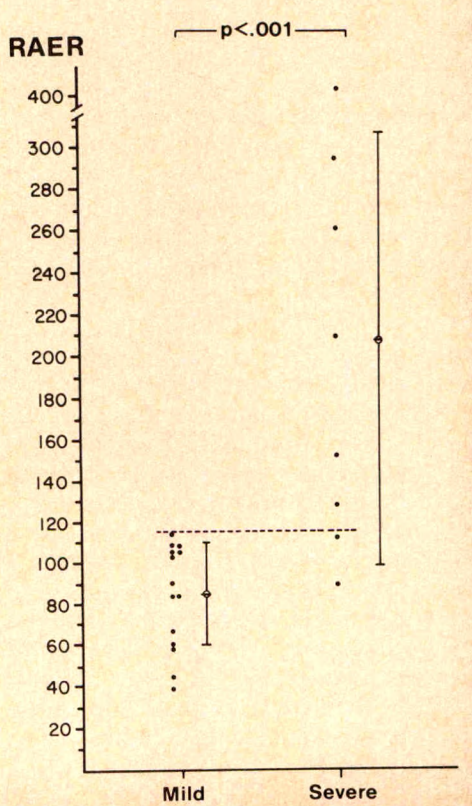

FIGURE 4. Right atrial expansion rate (RAER) in patients with mild and severe tricuspid regurgitation. See text for details.

TABLE I Two-Dimensional Right Atrial Indexes

	Cases	RAESV (ml)	RAEV (ml)	RAEF (%)	RAER (ml/s)
Group I	10	36 ± 13	15 ± 5	44 ± 14	39 ± 9
Group II	18	59 ± 17	18 ± 3	30 ± 9	–
Group IIIa	14	77 ± 55	30 ± 8	51 ± 19	84 ± 27
Group IIIb	8	155 ± 57	72 ± 25	50 ± 18	207 ± 108

RAEF = right atrial ejection fraction; RAER = right atrial expansion rate; RAESV = right atrial end-systolic volume; RAEV = right atrial emptying volume.

TABLE II Correlation of Right Atrial Emptying Volume With Presence of Tricuspid Regurgitation in Patients With Mitral Stenosis*

	Patients (n)	%
Sensitivity	18/22	82
Specificity	28/20	100
Positive predictive value	18/18	100
Negative predictive value	28/32	88
Predictive accuracy	46/50	92

* Right atrial emptying volume >26 ml.

The RA expansion rate similarly separated Group IIIb patients from Group IIIa patients (Fig. 4). None of the 14 Group IIIa patients and 6 of the 8 Group IIIb patients had a RA expansion rate >116 ml/s ($p < 0.001$).

Relation between mean right atrial and pulmonary pressure with right atrial emptying volume: The mean RA pressure corrected well with the RA emptying volume in the 36 patients who had RA catheterization measurements. The mean RA pressure ranged from 5 to 30 mm in the 24 patients with mitral stenosis (3 without and 21 with TR). The RA emptying volume correlated with mean RA pressure ($r = 0.71$, $p < 0.001$). Mean pulmonary artery pressure ranged from 11 to 68 mm Hg in Group III. There was no correlation between pulmonary artery pressure and RA emptying volume ($r = 0.06$).

Sensitivity, specificity and predictive accuracy differentiating severe from mild tricuspid regurgitation (Table II): The RA emptying volume was the most useful index in separating the 22 patients with pure mitral stenosis and TR from the 28 patients without TR. Using a value of 26 ml as a cut-off, a sensitivity of 82%, specificity of 100%, positive predictive value of 100%, negative predictive value of 88% and predictive accuracy of 92% was achieved in differentiating normal subjects from patients with mild TR. The RA emptying volume was useful in differentiating patients with severe TR from those with mild TR, with a sensitivity, specificity and predictive accuracy of 100% when a value of 40 ml was applied.

Discussion

The diagnosis of TR may be difficult by physical examination. Angiographic definition of TR is confusing because, depending on catheter position, factitious regurgitation may be produced. In addition, right ventricular angiography is invasive and not without risk to the patient. There appears to be no accepted standard for diagnosing TR.[10] Although contrast echocardiography may be useful in detecting TR, severe right heart failure, cardiac tamponade and arrhythmias may produce conflicting results.[3] Differentiating mild from severe TR is possible using inferior vena cava ultrasonography; however, differentiating normal subjects from patients with mild TR is not easy. Doppler echocardiography may offer an additional noninvasive approach to the diagnosis of TR and even allow its quantification.[11]

The present study describes the use of RA volumetric changes (the emptying volume) as a means of differentiating mild from severe TR. RA phasic changes may be more precise in assessing TR than inferior vena cava ultrasonography. This may be because the right atrium is the first reservoir that receives the regurgitant volume. Also, despite similar amounts of TR, a large, noncompliant right atrium may not transmit the reversal of flow into the vena cava as well as a small compliant right atrium.

Two-dimensional echocardiography is a good method of identifying the boundaries of the right atrium and measuring RA volume in almost all patients.[7] However, it is not the precise determination of RA volume measurement that is important, but rather, the phasic changes, which allow patients with TR to be differentiated from those without TR. Simply planimetering the RA area failed to differentiate these patients. There was no difference between patients with and those without AF with regard to RA emptying volume if TR was absent. Although right ventriculography was not performed in all patients, most Group I or II patients had normal clinical and physical examinations. The 3 patients with mitral stenosis in Group II who had no TR on right ventriculography all had an RA emptying volume of <20 ml.

There is considerable controversy over whether TR may be induced during AF. Ferrer et al[12] suggested that functional TR may be related to AF. The mechanism may be related to improper valve closure as a result of failure of the atria to contract before ventricular systole. However, recent work has shown no mitral and pulmonary venous regurgitation with AF in canine models.[13] Our studies show that AF is associated with a variable-sized right atrium but a small emptying volume. Therefore, the absent clinical, hemodynamic and right ventriculographic evidence of TR in these patients supports the concept that AF, as such, does not produce significant TR. This is in agreement with other investigators.[14] An increased RA emptying volume simply implies that there is additional contribution to inflow of the right atrium during systole. The fact that the RA ejection fraction was not increased in TR emphasizes that it is the magnitude of change in RA volume from diastole to systole that is representative of forward and retrograde flow into the right atrium during systole and not the ejection fraction.

This study has several limitations. First, the 22 patients with TR are a select group. They underwent right ventriculography because of suspected TR. Therefore, the sensitivity of our technique in predicting TR prospectively is not known. Second, patients with severe

MR have grossly enlarged atria that expand in systole. This may produce systolic bulging of the interatrial septum and, thus, affect the RA emptying volume. Third, problems are associated with using a light pen to calculate chamber volumes from stop-frame images. There is a parallax between the observed image on the curvilinear screen and the actual image. In addition, the endocardial borders, which seem obvious in real-time, may be indistinct in the stop-frame mode. Fourth, in cases of irregular AF with markedly irregular or slow rates (long-filling periods) or fast rates, representative cycles may not be available for computation. At least 4 consecutive beats should be analyzed and the mean value calculated.

Notwithstanding these limitations, the RA emptying volume is a useful 2-D echocardiographic measurement for detecting and quantitating the amount of TR that does not require intravenous contrast injections or contrast right ventriculography. AF appears to have little effect on RA expansion in the absence of TR.

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Influence of Volume Loading on Intraoperative Hemodynamics and Perioperative Fluid Retention in Patients With Valvular Regurgitation Undergoing Prosthetic Replacement

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Preload and afterload were controlled intraoperatively in 2 groups of patients with valvular regurgitation and congestive heart failure in order to determine the effect of fluid loading on weight gain and subsequent recovery. As a part of their anesthetic management before cardiopulmonary bypass, 16 patients were given 1 liter of crystalloid with nitroprusside infused at 1 μg/kg/min and 16 received 4 liters of crystalloid with nitroprusside at 4 μg/kg/min. Arterial and filling pressures were kept the same in both groups. Heart rate and vascular resistance became significantly lower and cardiac index and stroke volume significantly higher in the fluid-augmented group. The transition to cardiopulmonary bypass was smoother for the fluid-augmented patients. All patients survived, and 2 in each group were ventilated beyond 24 hours. The mean weight gain at surgery was the same in the 2 groups (3 kg). For the first 2 postoperative days, body weight remained unchanged and thereafter, both groups lost weight at 0.6 kg/day. Preoperative weight was reached on day 7 and discharge occurred on day 15, 2 kg below control. Thus, a modest operative weight gain in these patients is inevitable, benign, and independent of the volume of fluid infused before bypass.

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Sodium restriction and diuretics are a part of the medical management of patients with valvular regurgitation and congestive heart failure. Such therapy alleviates undesirable symptoms, but does so by reducing intravascular volume, often to the extent that an operative candidate comes to surgery in a relatively hypovolemic state.[1–3] For the patient with low-output failure, traditional anesthetic practice is to avoid fluid overload[4] and drugs that further depress the myocardium.[5] However, anesthetics without negative inotropic effects, such as narcotics or tranquilizers, fail to abolish the sympathetic response to surgical stimulation.[6] Peripheral vasoconstriction increases afterload, encourages regurgitant flow, reduces cardiac output and, in an already compromised heart, invites decompensation.[7] Vasodilators are used intraoperatively to overcome intense vasoconstriction;[6,8,9] but if intravascular volume has been depleted, capacitance vessels dilate, venous return decreases, and severe hypotension occurs before the beneficial effects of afterload reduction can be realized.[10] To maximize cardiac output and to provide a stable blood pressure during anesthesia and surgery, preload augmentation must accompany afterload reduction.[10,11] The postoperative consequences of fluid loading during surgery, however, remain undefined and of considerable concern. This study was undertaken to determine how patients with valvular regurgitation and heart failure would tolerate substantial intraoperative expansion of their intravascular volume.

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Methods

Thirty-two patients (16 in each group) who underwent prosthetic valve replacement had been in chronic congestive heart failure, with a diagnosis of pure or predominant valvular regurgitation established at cardiac catheterization by angiography. In the fluid-restricted group, 8 patients had mitral regurgitation, 5 aortic regurgitation and 3 both lesions. There were 10 women and 6 men, mean age 55 years. In the fluid-augmented group, 7 patients had mitral regurgitation, 6 aortic regurgitation and 3 both. There were 9 men and 7 women, mean age 58 years. All patients had depressed left ventricular function, normal coronary arteries, and were in New York Heart Association functional classification III or IV. All were taking digitalis and diuretic preparations and were judged to be in optimal condition for their elective cardiac surgery. No

TABLE I Preinduction Control Hemodynamic Data

	Fluid-Restricted	Fluid-Augmented
Heart rate (beats/min)	77 ± 5	78 ± 4
Arterial pressure (mm Hg)	83 ± 3	85 ± 4
Vascular resistance (unit)	39 ± 4	38 ± 3
Cardiac index (liters/min/m^2)	2.1 ± 0.2	2.2 ± 0.1
Stroke index (ml/beat/m^2)	28 ± 3	31 ± 3
Wedge pressure (mm Hg)	17 ± 2	18 ± 2
Central venous pressure (mm Hg)	5 ± 1	5 ± 1

Values are mean ± standard error.
No significant difference between fluid-restricted and fluid-augmented groups in any variable.

TABLE II Hemodynamic Data During Surgery

	Fluid-Restricted	Fluid-Augmented
Fluid volume (liters, total)	1.0 ± 0.2*	4.2 ± 0.5
Nitroprusside rate (μg/kg/min)	1.1 ± 0.7*	4.1 ± 0.8
Heart rate (beats/min)	95 ± 6†	81 ± 4
Arterial pressure (mm Hg)	71 ± 3	76 ± 3
Vascular resistance (unit)	33 ± 3*	23 ± 1
Cardiac index (liters/min/m^2)	2.1 ± 0.2*	3.1 ± 0.2
Stroke index (ml/beat/m^2)	22 ± 2*	39 ± 3
Wedge pressure (mm Hg)	16 ± 2	17 ± 2
Central venous pressure (mm Hg)	7 ± 1	7 ± 1

Fluid-restricted group significantly different from fluid-augmented group: * $p < 0.001$, † $p < 0.05$.

one was medicated preoperatively with vasodilators. Patients were allowed their usual diets and fluid intake until midnight of the day before surgery.

Premedication consisted of intramuscular morphine, 3 to 10 mg, and scopolamine, 0.3 to 0.5 mg. Monitoring included a percutaneous 20-gauge radial artery catheter and a No. 7Fr triple-lumen thermodilution Swan-Ganz catheter. Pressure was directly measured with Statham P23ID transducers, continuously displayed on an oscilloscope, and recorded by a Hewlett-Packard 8-channel strip-chart recorder. Cardiac output was determined in triplicate with an Edwards Laboratory cardiac output computer (9250A). Awake, preanesthetic control measurements were made after steady-state conditions had been achieved (Table I). These included heart rate, systemic arterial mean pressure, right atrial pressure, pulmonary artery mean pressure, pulmonary capillary wedge pressure and cardiac output. Standard formulas were used to compute cardiac index, stroke volume index and systemic vascular resistance index.

Anesthesia was induced gradually over 10 minutes with morphine (1 mg/kg) and diazepam (0 to 0.3 mg/kg) and then maintained with nitrous oxide (0 to 50%) in oxygen. Nondepolarizing muscle relaxants were given, patients were intubated, and ventilation was controlled mechanically with the arterial carbon dioxide partial pressure kept at about 35 torr. After surgical stimulation began, nitroprusside (0.2%) was administered by infusion pump. Its rate varied with the expansion of the intravascular volume and was adjusted to maintain wedge pressure at the control level. The volume of intravenous fluid given over the 90-minute span from induction of anesthesia until the onset of cardiopulmonary bypass differed in the 2 groups. Patients in the fluid-restricted group received Ringer's lactate solution at 10 ml/kg/h and a consequent nitroprusside infusion rate of approximately 1 μg/kg/min. Patients in the fluid-augmented group received Ringer's lactate solution at 40 ml/kg/h in the same time frame; this necessitated a mean nitroprusside infusion rate of about 4 μg/kg/min. A second set of hemodynamic measurements was obtained during the relatively stable surgical period just preceding cardiopulmonary bypass (Table II). Up to that point, management of the patients in the 2 groups differed only in the rate of the nitroprusside infusion and the volume of crystalloid they had received.

The extracorporeal circulation was primed with 1,400 ml of Ringer's lactate solution, to which 35 g of dextrose and 300 ml of 25% salt-poor normal serum albumin had been added. When cardiopulmonary bypass was instituted, nitroprusside was discontinued and fluid administration was carried out by the pump team, which was unaware of the study and which responded in routine fashion to alterations in pressure and flow. After bypass, while hemostasis was being accomplished, all of the perfusate remaining in the pump was reinfused into the patient. Thereafter, fluid administration was determined by the clinical judgment of anesthesiologists and surgeons not involved in the study. Each patient was weighed preoperatively and then daily for 10 days after surgery with a bedside sling-type calibrated electronic scale (Scale-Tronics 2001). Weighings took place in the morning, and patients wore only their hospital gowns (all bottles, tubing and catheters were lifted from the litter). Postoperatively, digitalis was restarted early, vasodilators were rarely used, and diuretics were given at the discretion of the referring physician. Results were analyzed by paired and unpaired t tests. A p value < 0.05 was considered significant.

Results

The awake control measurements, obtained on the day of surgery just before induction of anesthesia, were essentially the same in the 2 groups (Table I) and corroborate our clinical impression that the groups were comparable. A low-output state was evident, and the effectiveness of the preoperative diuretic therapy was manifested by the low central venous pressure.

The hemodynamic consequences of differing fluid loads and differing nitroprusside levels during stable anesthesia and surgery shortly before bypass are listed in Table II. Arterial pressure was reduced about 10 torr from control in both groups. Vascular resistance decreased to normal in the fluid-augmented group; however, it could not be so lowered in the fluid-restricted group and remained elevated by about 25%. In this latter, relatively hypovolemic group, increasing the speed of the nitroprusside infusion beyond a mean of 1 μg/kg/min produced hypotension. With nitroprusside, with the arterial pressure at 71 ± 3 mm Hg and vascular resistance still elevated, the fluid-restricted patients continued to have a low cardiac index, a very diminished stroke volume index and tachycardia. Patients who were fluid-augmented tolerated more afterload reduction with nitroprusside and had an improved hemodynamic pattern. Although wedge pressure was the same in both groups and had not changed from control at the time of the second measurement, 3 more liters of crystalloid filled the expanded vascular space of the fluid-augmented patients. As a result, cardiac index and stroke volume index increased to reach normal levels and heart rate did not vary.

Despite stopping nitroprusside at the onset of dilutional, hypothermic cardiopulmonary bypass, hypotension (defined as arterial mean pressure < 50 mm Hg) occurred in 10 of the 16 fluid-restricted patients (Table

TABLE III Cardiopulmonary Bypass Comparisons

	Fluid-Restricted	Fluid-Augmented
Lowest arterial pressure (mm Hg) recorded in first 15 minutes of bypass	49 ± 3	64 ± 3
Supplemental crystalloid (ml) required to maintain bypass pressure and flow	680 ± 120	60 ± 3
Lowest hematocrit (%) on bypass	27 ± 1	22 ± 1
Urinary output (ml) from anesthetic induction until end of bypass	500 ± 80	1,500 ± 180

Fluid-restricted group always significantly different from fluid-augmented group ($p < 0.001$).

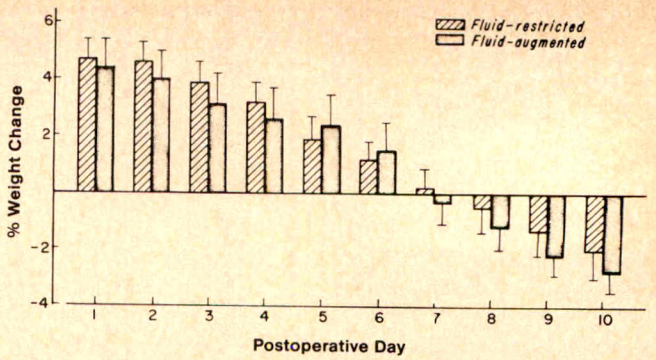

FIGURE 1. Postoperative body weight measured daily as a percent change from the preoperative value.

III). Pump flow was well maintained in all, and thus the pressure decrease was caused by a decrease in arterial vascular resistance. During the 10- to 15-minute equilibration period that followed the onset of bypass, vasopressors were given to 9 of the fluid-restricted patients, and a rapid infusion of Ringer's lactate solution was started in 14. In contrast, hypotension occurred and vasopressor therapy was instituted in 2 of the 16 fluid-augmented patients, with 3 receiving additional fluid loading. Hematocrit, obtained preoperatively and again after stabilization on bypass, decreased more in the fluid-augmented patients, 41 to 22% versus 40 to 27%. Urinary output from the start of anesthesia until the end of bypass was 1,500 ml in the fluid-augmented group and 500 ml in the fluid-restricted group.

All patients were ventilated postoperatively for at least 12 hours. Two patients in each group required ventilatory support for 2 days, but none became hypoxic or had evidence of more than minor pulmonary congestion.

Every patient in both groups gained weight at surgery. Postoperative body weights are depicted in Figure 1 as a percent change from the preoperative value. On no day were the mean weights of the 2 groups different. Mean weight gain at surgery averaged 3 kg and was the same in the 2 groups. For the first 2 postoperative days, body weight remained unchanged. Thereafter, body weights decreased steadily, and the rate of weight loss was the same in both groups. Patients lost about 0.6 kg/day. In both groups, preoperative body weight was reached on the seventh postoperative day. Patients were discharged on the fifteenth postoperative day in both groups; when they left the hospital, their weight was about 2 kg below control.

Discussion

We believe it is justified to conclude that operative weight gain is inevitable in these patients and the amount gained is independent of the volume of fluid infused before bypass. Patients with congestive heart failure did tolerate large intravenous fluid loads as a part of their anesthetic management, and neither intraoperative nor postoperative volume overload occurred in any of the fluid-augmented patients. In fact, it was the fluid-restricted patients who required intervention. In that group during cardiopulmonary bypass, the reservoir of the extracorporeal circulation became depleted, arterial pressure decreased, and volume supplementation was necessary for circulatory support.

Chronic preoperative diuretic therapy renders the ambulatory patient with congestive heart failure less dyspneic and more comfortable, but it does so by reducing the blood volume to a relatively depleted state, and thus by further decreasing cardiac output.[12] In response, there is a concomitant increase in circulating vasoactive substances and vascular resistance which tends to keep arterial pressure within normal limits.[12] Unfortunately, anesthetics and noxious surgical stimuli make vascular tone highly labile and thus disrupt the tenuous hemodynamic balance achieved in these patients by careful preoperative medical management. Cardiopulmonary bypass is an abrupt and even more extreme circulatory alteration. On the one hand, blood flow is mechanically maintained above that necessary to fulfill oxygen requirements. Edema fluid is mobilized from congested tissues and urinary output increases. On the other hand, body temperature is acutely lowered, severe dilutional anemia occurs and the lungs are excluded from the circulation. Initially, vascular tone decreases to a subnormal level,[13] arterial pressure falls, and a new relation forms between circulating blood volume and intravascular space. Later, especially with rewarming on bypass, catecholamines and other vasoactive substances are released increasing blood levels by several-fold.[13,14] Vascular resistance again becomes excessive, arterial pressure increases, and vasodilators are often indicated to improve the circulation and permit weaning from bypass.[14] In the immediate postoperative period after valve replacement, cardiac output remains low, often requiring support,[15] and only gradually improves over the succeeding months.

The question of how best to support a sagging and unstable circulation has intrigued clinicians since intervention became possible. Today in the acute-care setting, vasodilators have become prominent in the therapy of cardiac failure;[7] for not only is the circulation improved, but myocardial oxygen consumption does not increase.[12] However, vasodilators alone may not provide sufficient cardiovascular support, and then one must choose additional therapy. As a measure of the cost of intervention, Sarnoff et al[16] demonstrated that much

more myocardial energy was expended doing pressure as opposed to flow work. Preload augmentation can triple cardiac output and stroke work with only a minor increase (23%) in myocardial oxygen consumption.[17] Alternatively, catecholamines and other inotropic agents, which increase contractility and often afterload and heart rate as well, profoundly increase myocardial oxygen consumption.[12]

In conclusion, we have shown that intraoperative regulation of preload and afterload can effectively and safely enhance cardiac function in patients with heart failure. However, instead of acute intraoperative fluid loading, we suggest that expansion of the intravascular volume be attempted preoperatively, when patients can be gradually changed from a regimen of diuretics and sodium restriction to one of oral vasodilators and rehydration. Oral vasodilators have been somewhat of a disappointment as long-term therapy for cardiac failure because the initial improvement often wanes with time;[18,19] but perhaps in the immediate preoperative period they can be used to real advantage by facilitating the inevitable increase in blood volume that accompanies surgery.

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Mitral Valve Prolapse Syndrome: Analysis of 62 Patients Aged 60 Years and Older

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Sixty-two patients diagnosed as having mitral valve prolapse, 60 to 81 years old, presented with disabling chest pain (20), symptoms of arrhythmias including palpitations and syncope (16), or mitral regurgitation (MR) with symptoms of congestive heart failure (26). The diagnosis of MVP was made on the basis of a combination of classic auscultatory, echocardiographic and angiographic findings. Thirteen of the 20 patients with chest pain had normal coronary angiograms and 7 had significant coronary artery disease (CAD). Patients with CAD could not be differentiated by clinical presentation alone. Furthermore, the incidence and types of arrhythmias, the presence of a positive stress test, and hemodynamic findings were similar in all patients in this group whether or not CAD was present. The 16 patients with palpitations had a broad spectrum of rhythm disorders, including both supraventricular and ventricular arrhythmias. Two patients had prehospital "sudden death" and 2 others had systemic emboli. Twenty-one of the 26 patients with MR had valve surgery. Intraoperatively the valves were described as enlarged, floppy and with redundant leaflets. Histologic examination showed extensive "myxomatous" changes throughout the valve leaflets.

Thus, mitral valve prolapse is a cause of symptomatic heart disease in the elderly. It has a predictable pattern of clinical presentation and should be considered in the differential diagnosis of older patients with disabling chest pain and arrhythmias and as the cause of progressive or severe MR.

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Mitral valve prolapse (MVP), a well described clinical entity with characteristic auscultatory, echocardiographic and angiographic findings, usually becomes clinically manifest in the third through the fifth decades of life.[1–9] Most patients initially present with symptoms of chest pain and palpitations.[2,3,6] MVP is also a very common cause of clinically recognizable mitral regurgitation (MR) murmurs, which are usually preceded by nonejection systolic clicks.[3,5,6] Based on surgical and postmortem examinations, the primary pathologic process of MVP has been attributed to myxomatous degeneration of the mitral valve leaflets.[7–10] Although the prognosis in the majority of patients with the MVP has been described as good,[11–14] the long-term natural history of the MVP is not well defined, and few studies have directly addressed the presence and clinical presentation of patients with MVP who are ≥60 years.[15,16]

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The purpose of this study was to define the clinical spectrum of patients with MVP in the seventh through ninth decades of life and to gain a greater insight into the natural history of MVP.

Methods

All patients were ≥60 years old. The diagnosis of MVP was based upon auscultatory findings of midsystolic clicks or late systolic or holosystolic murmurs with typical postural variations,[4,16,17] M-mode echocardiographic findings of mid- to late posterior motion of the posterior mitral valve leaflet in systole,[7] and left ventricular angiographic presence of systolic posterior excursion of the mitral valve leaflets beyond the mitral valve annulus.[3,8,18] Each patient had at least 2 of these findings.

Sixty-two patients, aged 60–81 years, were included in this study. All patients were evaluated at University Hospital because of debilitating cardiac symptoms, which included 20 patients (15 women, 5 men) with disabling chest pain, 16 patients (12 women, 4 men) with symptoms suggestive of arrhythmias and 26 patients (16 men, 10 women) with symptoms of congestive heart failure and the murmur of MR. Fifty-two patients had technically adequate M-mode echocardiograms. Fifty-six patients underwent cardiac catheterization including coronary angiography. Significant coronary

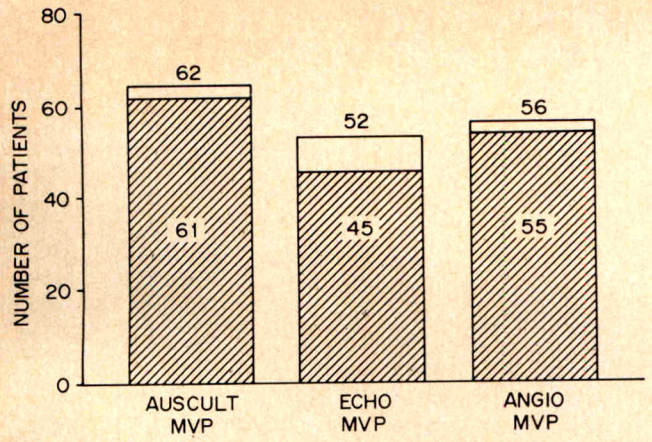

FIGURE 1. The sensitivity of the individual methods used to diagnose mitral valve prolapse (MVP). The number of patients with satisfactory examinations is listed at the top of each bar. The number of patients in whom the examination indicated MVP is listed in the shaded area of the bars. Angio = left ventricular angiography; auscult = auscultatory exam; echo = echocardiography.

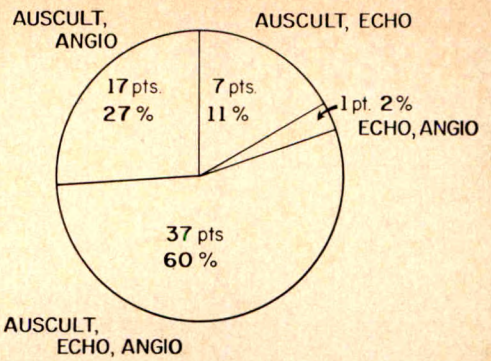

FIGURE 2. The basis for the diagnosis of mitral valve prolapse (MVP) and the number of patients in whom each of the diagnostic methods indicated MVP. Thirty-seven patients (60%) had evidence of MVP by all 3 examinations, whereas the diagnosis of MVP in 25 patients (40%) was based on a combination of 2 of the 3 methods that indicated MVP. Angio = left ventricular angiography; auscult = auscultation; echo = echocardiography.

artery disease (CAD) was defined as >50% transluminal narrowing of at least 1 major coronary vessel.

Results

Diagnosis: The 62 patients included 25 between the ages of 60 and 64 years old, 22 between 64 and 69 years, 6 between 70 and 74 years and 9 ≥75 years. These patients represented 4% of all adult patients who underwent cardiac catheterization in our laboratories during the study period.

The results of the auscultatory findings, echocardiography and left ventricular angiography are shown in Figure 1. The cardiac physical examination was abnormal in 61 of 62 patients. Auscultatory findings in the 36 patients with chest pain and symptoms of arrhythmias included 30 with mid- to late systolic murmurs associated with nonejection clicks and 5 with midsystolic clicks without murmurs. All 26 patients with congestive heart failure symptoms had a holosystolic murmur of MR.

Echocardiography demonstrated MVP in 45 of the 52 patients who had adequate M-mode echocardiograms. Angiographic prolapse was identified in 55 of the 56 patients who underwent cardiac catheterization; 44 had angiographic MR. Thirteen of the 56 patients also had evidence of significant CAD.

The combination of abnormal auscultatory, echocardiographic and angiographic findings is shown in Figure 2. Thirty-seven patients had MVP by auscultation, echocardiography and left ventricular angiography; 17 by auscultation and left ventricular angiography; 7 by auscultation and echocardiography; and 1 by echocardiography and left ventricular angiography.

Patients with mitral valve prolapse and chest pain: Twenty patients with MVP presented with disabling chest pain as their primary complaint, only 1 of whom had a history of a myocardial infarction. The average age was 64 years (range 60 to 82) and the average duration of symptoms was 4 years. All patients had coronary angiography, and the angiogram demonstrated CAD in 7. The resting electrocardiograms in the 13 patients without CAD revealed that 3 patients had left anterior hemiblock, 1 intraventricular conduction delay, 2 subendocardial ischemia, 2 nonspecific ST changes and 2 premature ventricular contractions (PVCs); 3 patients had normal electrocardiograms. Of the 7 patients with CAD, 2 showed left anterior hemiblock, 2 subendocardial ischemia, 1 inferior infarction and 1 nonspecific ST changes; 1 patient had a normal electrocardiogram.

Adequate treadmill stress tests were obtained in 7 patients; 4 indicated ischemic ST-segment changes, defined as >1 mm of ST-segment depression 0.08 second after the J point. Two of these 4 patients had CAD.

Twenty-four-hour Holter monitoring in 7 patients without CAD showed arrhythmias in all 7 patients, including paroxysmal atrial fibrillation in 1, rare PVCs in 1 and frequent PVCs (>10/minute) in 4, including ventricular bigeminy and ventricular tachycardia. Ambulatory monitoring in 3 patients with CAD disclosed premature atrial contractions (PACs) in 1, atrial fibrillation in 1 and rare PVCs in 1.

Echocardiographic MVP was seen in 14 of the 17 patients, 9 of 11 without and 5 of 6 with CAD.

Catheterization data for these patients with chest pain are shown in Table I. The data were remarkably

TABLE I Catheterization Data From Patients With Chest Pain

	All Patients (n = 20)	No CAD (n = 13)	CAD (n = 7)
Ejection fraction	69%	69%	70%
LVEDV (ml/m^2)	70	72	67
Post-angio LVEDP >24 mm Hg (no. of pts)	12	7	5
Angiographic MVP (no. of pts)	20	13	7

CAD = coronary artery disease; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; MVP = mitral valve prolapse.

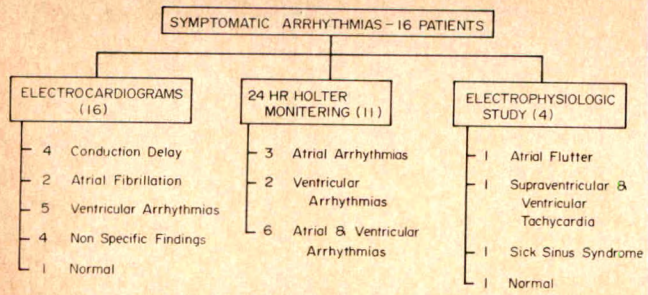

FIGURE 3. The methods used to identify the rhythm disorders in the 16 patients with palpitations and syncope and the type of arrhythmias.

similar whether or not CAD was present. Of the 7 patients with CAD, 1 had 1-vessel, 4 had 2-vessel and 2 had 3-vessel disease.

Patients with mitral valve prolapse and symptoms of arrhythmias: Sixteen patients presented with symptoms suggestive of arrhythmias, including 11 with palpitations and 5 with syncope. None of these patients had a history of a myocardial infarction. The average age of these patients was 66 years and the average duration of symptoms was 12 years. Two patients had clinical evidence of systemic emboli, both with visual blurring, visual field defects, atrial fibrillation and no evidence of cerebrovascular disease. Two of the 5 patients with syncope required cardiopulmonary resuscitation.

The diagnoses of the specific types of arrhythmias shown in Figure 3 were made from the resting electrocardiogram, 24-hour Holter monitoring or electrophysiologic studies. The resting electrocardiograms were abnormal in 15 patients. The ventricular arrhythmias seen on the electrocardiograms included ventricular tachycardia in 1 patient, frequent PVCs of >10/min in 2 patients and occasional PVCs in 2.

Twenty-four-hour Holter monitoring in 11 patients revealed supraventricular arrhythmias in 3, including paroxysmal atrial fibrillation, frequent PACs and paroxysmal supraventricular tachycardia. Two patients had ventricular arrhythmias alone identified as frequent PVCs. Six patients demonstrated both supraventricular and ventricular arrhythmias, which included sinus node arrest with frequent PVCs in 1, frequent PACs with frequent unifocal PVCs in 2, supraventricular tachycardia and frequent PVCs in 2 and ectopic atrial rhythm with multifocal PVCs in 1.

Four patients had electrophysiologic studies: 1 who developed atrial flutter when stimulated with PACs, 1 who developed both supraventricular and ventricular tachycardia and 1 who had significant sinus node disease; 1 showed no abnormalities.

Ten patients had cardiac catheterization and coronary angiography. Two patients had 1-vessel CAD. The average ejection fraction of all 10 patients was 64% and the left ventricular end-diastolic volume index was 70. The postangiographic left ventricular end-diastolic pressure was abnormally increased in 5 patients, with values of 24 to 36 mm Hg. Angiographic MVP was demonstrated in 9 of the 10 patients.

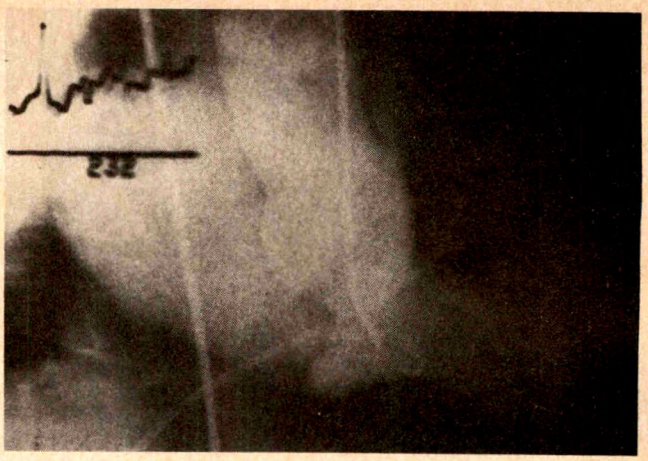

FIGURE 4. Thirty-degree right anterior oblique left ventriculogram, which demonstrates significant angiographic mitral regurgitation secondary to a prolapsing mitral valve with ruptured chordae. The ruptured chordae cannot be seen in this view. The left atrium is considerably enlarged.

Patients with mitral regurgitation and congestive heart failure: Twenty-six patients had significant MR and symptoms of congestive heart failure. The mean age of these patients was 68 years (range 60 to 81). Twenty-two of the 26 had a history of a heart murmur. Twelve patients had murmurs detected before age 30 years, 7 patients at 31 to 60 years and 3 patients above age 60 years.

Of these 26 patients, 20 had radiographic cardiomegaly. The resting electrocardiograms were abnormal in 25 patients; the most common abnormality was atrial fibrillation, which was seen in 13 patients. Five patients also had electrocardiographic criteria of left ventricular hypertrophy. Thirteen of 24 patients with adequate echocardiograms had MVP and 5 others had a flail mitral valve leaflet in addition to MVP.

The results of cardiac catheterization performed in all 26 patients are shown in Table II. Angiographic MVP with MR was seen in all 26 patients. Tricuspid valve

TABLE II Catheterization Data From Patients With Mitral Regurgitation

Hemodynamic Data	All Pts (n = 26)	MVR (n = 21)	No MVR (n = 5)
Ejection fraction	67%	68%	63%
LVEDV (ml/m^2)	119	125	90
Post angio LVEDP >24 mm Hg (no. of pts)	12	9	3
PCW pressure (mm Hg)	18	19	11
V wave (mm Hg) in PCW	34	38	20
Left and right ventricular angiography (no. of pts)			
MR	26	21	5
MVP	26	21	5
TVP	6/12	6	0
Coronary angiography (no. of pts)			
No CAD	22	17	5
CAD	4	4	0

CAD = coronary artery disease; MR = mitral regurgitation; MVR = mitral valve replacement; PCW = pulmonary capillary wedge; TVP = tricuspid valve replacement.

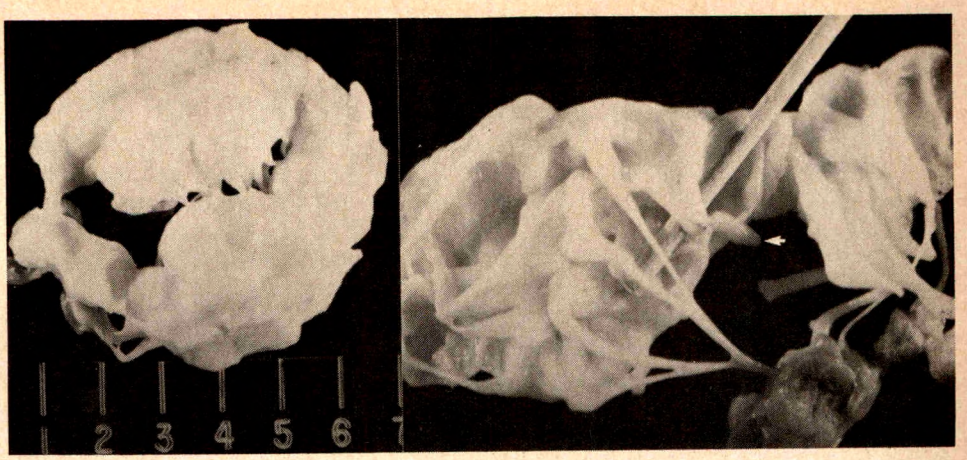

FIGURE 5. Left, The gross appearance of an abnormally large floppy valve with redundant leaflets as seen from the atrial side. The diameter and cross-sectional area of the valve are abnormally increased. **Right,** the same valve as seen from the ventricular side, again demonstrating the redundancy of the leaflets. The presence of several ruptured chordae are also seen (**arrow**).

prolapse was demonstrated in 6 of the 12 patients who had a right ventricular angiogram. Four patients had CAD, but none had a totally occluded vessel and none had evidence of a previous myocardial infarction.

In 21 patients, progressive clinical deterioration due to MR was so severe that cardiac surgery was performed. Table II lists the hemodynamic and angiographic data in these patients. Figure 4 shows the angiographic appearance of a severely regurgitant prolapsing mitral valve.

Three patients had additional cardiac surgery, including 1 who had aortic valve replacement for aortic insufficiency and 2 coronary artery bypass grafts. Two patients died postoperatively, 1 from congestive heart failure and 1 from sepsis. All surviving patients were significantly improved symptomatically at the time of hospital discharge and were in New York Heart Association functional class I or II.

Pathologic observations of the mitral valve in operative patients: All surgically excised mitral valves were described by the surgeon as floppy with redundancy of the valve leaflets. A flail leaflet was present in 11 patients. Pathologic examinations performed on 19 of the 21 valves revealed enlarged anterior and posterior leaflets and an enlarged mitral valve diameter, which averaged 4.5 cm for all valves. Figure 5 demonstrates the gross pathologic findings of a severely myxomatous valve. This valve is the same valve shown angiographically in Figure 4. The histologic findings of all valves included severe myxomatous changes with disarray of collagen. Such changes were extensively present throughout the valve leaflets and, in the majority of instances, also involved the chordal structures. The gross morphologic and histologic changes are very similar to those described in a recent study from this institution that involved surgically excised valves from patients with symptomatic MR.[19]

Discussion

The occurrence, frequency and clinical characterization of MVP in elderly patients has not been well defined. The present study identified MVP as a cause of symptomatic heart disease associated with significant morbidity in elderly patients who presented in a clinically predictable pattern with disabling chest pain, symptomatic arrhythmias and MR with congestive heart failure.

The reported prevalence of MVP in young women is 6 to 17%, based on auscultatory and M-mode echocardiographic findings.[20,21] Several postmortem studies have reported prevalence rates of 1 to 5% in older patients.[22,23] Pomerance[10] reported 35 cases of mucoid degeneration of the mitral valve in 3,083 adult necropsies and described similar changes in 4.5% of elderly patients with systolic murmurs.[22] Davies et al[23] reported that the overall incidence of severely floppy mitral valves was 4% in men and 5% in women in 1,984 routine hospital necropsies.[23] These severely floppy valves were not apparent until after age 40 years, and the incidence of severely floppy valves increased with age. The findings of Davies et al are consistent with the incidence of MVP (4%) seen in patients >60 years who underwent studies in our catheterization laboratories.

The results of our clinical study extend the necropsy findings of Pomerance[10] and Davies et al[23] by providing further evidence for MVP as a cause of symptomatic cardiovascular disease in elderly patients. Two additional studies also considered the occurrence of the MVP in the elderly. Tresch et al[15] reported 40 patients >60 years with echocardiographic evidence of MVP. Twenty-nine presented with cardiac symptoms of chest pain, palpitations or congestive heart failure. Higgins et al[16] described clinical findings in 40 men ≥50 years with echocardiographic MVP and with symptoms of chest pain and palpitations. Nineteen had arrhythmias and 21 left ventricular hypertrophy. Neither of the above studies provided information about hemodynamics nor the presence or absence of coronary disease; however, the clinical findings were very similar to those of patients in our study. It should be emphasized that our study is not a natural history study, but a study that defines a group of symptomatic elderly patients with auscultatory, echocardiographic and angiographic findings similar to those found in younger patients with MVP. Whether these older patients represent a progression of MVP with aging cannot be stated with certainty. However, several important aspects of our study deserve further emphasis.

Mitral valve prolapse and chest pain: Approximately one third of our patients presented with disabling chest pain, a well described symptom in younger patients with MVP.[2,3,6] Coronary angiography identified 7 patients with significant CAD, none of whom had left ventricular wall motion abnormalities or a history of myocardial infarction. Because the clinical presentation and laboratory data were remarkably similar in the patients with chest pain whether or not CAD was present, patients with CAD could be accurately identified only by performing coronary angiography.

The coexistence of MVP and CAD in the same patients has been described,[24] and CAD has been implicated as a cause of MVP. Although the cause of the MVP in our patients with CAD cannot be definitely established, this group of patients does point out problems in the differential diagnosis of chest pain in the elderly and emphasizes the necessity of thorough clinical evaluation.

Mitral valve prolapse and arrhythmias: Fifteen patients presented initially with symptoms suggestive of arrhythmias, a common finding in younger patients with MVP.[25] The diagnosis of these rhythm disorders was usually apparent from the resting electrocardiogram, 24-hour Holter monitoring or electrophysiologic studies. The types of rhythm disturbances were similar to those reported to occur in patients with MVP.[25] Of particular note are the 2 patients who survived sudden death, both of whom had normal coronary artery anatomy. Sudden death is rare, but has been reported to occur with MVP.[26]

Although multiple causes of arrhythmias exist in this age group, MVP was considered a likely cause of arrhythmias in our patients, particularly in the absence of other definable types of heart disease. Neither of the 2 patients with 1-vessel coronary disease had angina or had sustained a previous myocardial infarction, and none of the 5 patients without catheterization studies had chest pain.

Two patients in this group and another patient in the chest pain group had clinical findings consistent with systemic embolization. The presence of atrial fibrillation in 2 of our 3 patients introduces another potential factor. The association between MVP and systemic embolization has been recognized; however, this relationship is unclear.[27]

Mitral valve prolapse, mitral regurgitation and mitral valve replacement: The 26 patients with the murmur of MR and symptoms of congestive heart failure may contribute to the understanding of the natural history of MVP in a select group of patients. A history of a heart murmur in 22 of these patients, and particularly in the 12 patients who had a known heart murmur before age 30 years, suggests that a less severe abnormality of the mitral valve existed throughout their earlier years. The presentation of these patients at an older age with congestive heart failure and clinically recognizable MR suggest that this "benign" mitral valve abnormality progressed to a severe lesion with aging. These observations imply that the natural history of MVP in certain patients may include progression to clinically significant MR.

Several additional clinical findings in these patients with MR must be emphasized, including the high incidence of atrial fibrillation, the coexistence of tricuspid valve prolapse, the low incidence of CAD and the male predominance among patients who received mitral valve surgery. Atrial fibrillation was very common in the patients who presented with congestive heart failure and severe MR (13 of 26 patients). This rhythm disturbance also occurred frequently in the studies of Higgins et al[16] (14 of 40 patients) and Ranganathan et al[18] (11 of 16 patients). Atrial fibrillation may have contributed in part to the sudden clinical deterioration in many of these patients.

The association of tricuspid valve prolapse with MVP is well known[28] and implies multivalvular involvement in patients with MVP. However, the predominant hemodynamic lesion in our patients was MR and the degree of tricuspid regurgitation was only mild to moderate.

CAD was not an important factor in the clinical presentation of these patients, since the incidence of CAD was low and none of the patients with CAD had chest pain or evidence of a myocardial infarction. Cardiac catheterization data indicated excellent left ventricular function in the overall group, although the left ventricular end-diastolic volumes were abnormally increased, as might be expected.

The incidence of MVP is significantly higher in the female population in the younger age group.[2,6] This female preponderance also occurred in our patients with chest pain and arrhythmias. However, this sexual preponderance was reversed in the group with severe MR.

The pathologic findings of extensive myxomatous changes in the surgically excised mitral valves in our patients are important relative to necropsy studies of mitral valves.[10,23,29] Nonspecific myxomatous changes in the mitral valve leaflets occur with aging, but are usually minor and not clinically significant.[23,29] The incidence of extensive myxomatous changes that involve the mitral valve in older patients is low, and such changes are unlikely to be the result of aging alone.[29] Furthermore, Davies et al[23] showed that severely floppy valves were direct causes of death and that patients with such valves were highly likely to have had a known heart murmur many years before their deaths.[23]

Severe myxomatous changes in mitral valves excised from 12 patients, mean age 51.5 years, have been reported from our laboratory.[19] Those valves were clearly differentiated from control valves on the basis of increased surface area, increased diameter and decreased density of the affected valve. Histologically, these valves showed more extensive myxomatous changes and, more specifically, collagen dissolution. The pathologic studies of Pomerance,[10,29] Davies et al[23] and King et al[19] further suggest that severely myxomatous mitral valves represent progressive disease of the valve rather than a process that occurs naturally with aging.

Such pathologic studies are of great clinical relevance because myxomatous mitral valves that produce severe MR have become one of the more common indications for mitral valve surgery in the elderly patient. Such observations are supported by several pathologic studies of surgically excised mitral valves that are characterized by extensive myxomatous changes.[9,23,28,30,31] Particularly noteworthy are the studies of Davies et al,[23] who found such changes in 44 valves, and Salamon et al,[30] who replaced 66 myxomatous mitral valves in patients whose average age was 58 years. Thus, the results of our study add a clinical dimension to the surgical pathologic studies and confirms the presence of severe myxomatous mitral valve disease that causes severe MR in older persons.

Implications of mitral valve prolapse with respect to natural history: The results of this study should not be interpreted as a true reflection of the natural history of patients with MVP. Nevertheless, there is accumulating evidence that MVP is an entity to be considered as a cause of symptomatic heart disease in the elderly patient. The necropsy studies of Pomerance[10,22,29] and Davies et al,[23] as well as the study of King et al,[19] this study, and other clinical studies identifying the MVP in elderly patients[15,16] and the pathologic findings of surgically excised myxomatous valves,[28,30,31] may have important implications with respect to the natural history of the MVP.

Heretofore, natural history studies have emphasized the benign nature of MVP.[11–14,32] Although it seems justifiable to consider MVP as benign and to reassure patients that their prognosis is good, the many reports in the literature about the benign course of MVP are unsupported by long-term data. MVP carries a significant morbidity in an as yet undetermined number of patients. In a study of 62 patients by Allen et al,[12] 3 patients died of cardiac-related causes. Mills reported 8 complications in 53 patients, 2 of whom died suddenly and 5 of whom developed progressive MR.[13] Koch and Hancock[32] followed 40 patients for 10 years and reported 5 patients with sudden death, 2 with congestive heart failure and 1 patient with chronic atrial fibrillation.[32] Numerous investigators have also reported complications such as sudden death,[2,6,26] bacterial endocarditis[12,13] and severe MR requiring mitral valve replacement[9,13,18,28,30,31] in patients with MVP. Particularly noteworthy in this regard are 2 studies, a recent report by Clemens et al,[33] who reemphasized the importance of bacterial endocarditis as a complicating factor with MVP, and the necropsy findings of Davies et al,[23] who implicated severely floppy mitral valves as a direct cause of death from bacterial endocarditis and severe MR.

The results of our study indicate that certain patients with MVP may be at risk later in life of developing complications such as disabling chest pain, cardiac arrhythmias, arterial emboli or progressive MR with congestive heart failure requiring consideration for mitral valve surgery. There is a gap in our understanding of the pathogenesis and natural history of this entity, and we cannot identify younger patients who may be likely to develop complications later in life.

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Value of Isometric Exercise Testing During Cardiac Catheterization in Mitral Stenosis

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To examine the value of preoperative isometric exercise testing during cardiac catheterization in patients with mitral stenosis, the isometric handgrip exercise test was performed on 28 patients during preoperative diagnostic catheterization. Eighteen patients who subsequently underwent mitral valve surgery were recatheterized and reevaluated clinically 12 months after operation. Preoperatively, the patients were divided into 2 groups: 16 whose mean mitral valve pressure gradient increased >4 mm Hg during isometric exercise (group A) and 12 whose pressure gradient decreased or increased <4 mm Hg (group B). The ejection fraction remained unchanged and the peak systolic pressure/end-systolic volume ratio increased during isometric exercise in group A ($p < 0.001$). In group B, the ejection fraction decreased ($p < 0.001$) and the peak systolic pressure/end-systolic volume ratio remained unchanged. In the total group, a positive correlation existed between the change in mean mitral valve pressure gradient during isometric exercise and the changes in measures of left ventricular function during exercise. The patients in group A had a significant improvement in both symptoms and in exercise tolerance as determined by symptom-limited bicycle ergometry after surgery. The patients in group B showed minimal or no symptomatic improvement and their exercise tolerance did not improve. The change in mitral valve pressure gradient during isometric exercise appears to reflect the left ventricular response to exercise.

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Isometric exercise reveals left ventricular (LV) dysfunction and increases the mitral valve pressure gradient in some patients with mitral stenosis (MS).[1,2] The isometric handgrip exercise test can be performed easily and safely during cardiac catheterization without causing major disturbances in the pressure recordings.[3,4] The present study evaluates whether the measurement of mitral valve pressure gradient during isometric handgrip exercise would give useful information for therapeutic decisions regarding patients with MS.

Patients and Methods

Patients: A consecutive series of 28 patients with clinically and echocardiographically suspected significant MS underwent cardiac catheterization and a concurrent handgrip test. Patients with more than trivial mitral regurgitation (regurgitant fraction >0.20) or aortic valve disease (>10 mm Hg peak systolic pressure gradient across the aortic valve or clinical signs of aortic regurgitation) were excluded. Ten patients underwent open mitral commissurotomy and 8 patients mitral valve replacement. The patients underwent recatheterization and were reevaluated clinically 12 months after surgery.

The patients were divided preoperatively into 2 groups according to the change in the mean mitral valve pressure gradient during isometric exercise. Sixteen patients whose valvular gradient increased >4 mm Hg during isometric exercise formed group A and 12 patients whose pressure gradient increased <4 mm Hg or decreased formed group B. The mean age of the patients in group A, which included 9 females and 4 males, was 49 ± 13 years, and that of group B, which included 8 females and 4 males, was 51 ± 9 years. Nine patients in group A and 5 in group B had atrial fibrillation; the others were in sinus rhythm. None of the patient had any conversion of atrial fibrillation to sinus rhythm or vice versa after surgery. Most of the patients were receiving digitalis therapy during the pre- and postoperative studies. None were receiving beta-blocking or vasodilating agents. Functional impairment was determined by the New York Heart Association classification of the grade of symptoms and by the symptom-limited bicycle exercise test both pre- and postoperatively. The bicycle exercise test was performed using a Godard-Statham electrically braked bicycle ergometer. The work load was increased progressively (15 W/min in men and 10W/min in women) until symptoms of dyspnea or exhaustion. The maximal work load achieved was then used for analysis of data. All the patients gave informed consent to the exercise tests and catheterization studies.

Invasive studies: Pre- and postoperative right and left-sided cardiac catheterizations were performed through the cubital vein and the brachial artery approach. Right atrial pressures, pulmonary pressures and pulmonary capillary wedge pressures were recorded with a Statham P23Ia transducer. Left ventricular (LV) pressures were recorded with a Statham P23Ia transducer or, whenever possible, with a high-fidelity Millar tip transducer, with pressures matched against fluid-filled luminal pressures. A data acquisition system (Hewlett-Packard 5600B) was used for the standard recording of pressures. Selective biplane LV cineangiography

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TABLE I Preoperative Hemodynamic Data at Rest and During Isometric Exercise

	HR (beats/min)		LVPSP (mm Hg)		LVEDP (mm Hg)		MV-GRAD (mm Hg)		MVA (cm^2)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Group A	77 ± 16	98 ± 19	124 ± 25	147 ± 32	10 ± 4	11 ± 4	12 ± 4	21 ± 5	1.5 ± 0.4	1.5 ± 0.4
	<0.001		<0.001		NS		<0.001		NS	
Group B	74 ± 16	93 ± 16	129 ± 19	149 ± 19	13 ± 4	18 ± 4	9 ± 4	10 ± 5	1.6 ± 0.4	1.5 ± 0.5
	<0.001		<0.001		<0.001		NS		NS	

Values are mean ± SD; p values with paired *t* test between data at rest and during exercise.
HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure; MV-GRAD = mean mitral valve pressure gradient; MVA = mitral valve area.

TABLE II Preoperative Angiographic Data at Rest and During Isometric Exercise

	ESVI (ml/m^2)		EDVI (ml/m^2)		EF (%)		PSP/ESVI ($mm\ Hg/ml \cdot m^{-2}$)		SV (ml)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Group A	34 ± 10	33 ± 9	82 ± 14	79 ± 13	59 ± 7	59 ± 7	4.0 ± 1.4	4.9 ± 1.5	84 ± 17	82 ± 18
	NS		NS		NS		<0.001		NS	
Group B	42 ± 32	49 ± 31	89 ± 25	89 ± 25	54 ± 7	47 ± 8	3.4 ± 1.3	3.5 ± 1.5	87 ± 22	72 ± 20
	<0.001		NS		<0.001		<NS		<0.005	

Values are mean ± SD; p values with paired *t* test between data at rest and during exercise.
EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; PSP/ESVI = ratio between peak systolic ventricular pressure and end-systolic volume index; SV = stroke volume.

was performed in the 45° right anterior oblique position. Coronary angiography was performed on 6 patients with symptoms of angina pectoris (5 in group B and 1 in group A) using the Judkins technique. No coronary artery bypass grafts were performed during surgery.

Isometric exercise tests: After pre- and postoperative ventriculography, LV pressures were recorded until they returned to baseline levels. Then, at least 20 minutes after resting cineangiography, the patients were asked to perform a handgrip test as described previously.[5] LV pressures, mean mitral valve pressure gradient and heart rate were determined every minute for 4 minutes during sustained handgrip. After 4 minutes, and with the patients still performing the grip, LV cineangiography was again carried out.

Measurements: LV volumes were measured from 1 or 2 representative beats and the postextrasystolic beats were discarded. In the patients with atrial fibrillation, the volume measurements were taken on the beats that most closely approximated the average RR interval for the basal ventricular response. In the postoperative angiograms, the cycle length chosen for analysis was that which most resembled that of the preoperative cycle. The contours of the left ventricle were digitized at biplane with a sonic pen on the projection screen using HP 5600B system and biplane area-length method for volumes.[6] The LV pressure curve was recorded simultaneously with the angiogram, or just before it when fluid-filled catheters were used, at a paper speed of 150 mm/s and was digitized and synchronized with the corresponding volume data with the aid of the HP 5600B system. The mean mitral valve pressure gradient and the diastolic filling period were measured both at rest and during isometric exercise by simultaneously recording pulmonary capillary wedge and LV pressures. The mitral valve area was then calculated from the modified Gorlin formula[7] using both the angiographically determined and the Fick method–determined total LV stroke volume to represent the flow of the orifice. The mitral regurgitant fraction was measured by subtracting the stroke volume, determined by the Fick method, from the total LV stroke volume.

Calculations: Statistical analysis was performed by using the paired *t* test to compare the individual data at rest with those obtained during isometric exercise and the preoperative data with the postoperative data. The Student *t* test was used to compare changes between the 2 groups. Linear regression analysis was used to calculate correlations.

Results

Pre- and postoperative hemodynamic data: A summary of preoperative hemodynamic data at rest and during isometric exercise is presented in Table I. Preoperatively, heart rate and LV peak systolic pressure increased significantly and equally in both groups during exercise. LV end-diastolic pressure remained unchanged in group A, but increased significantly in group B. LV end-diastolic pressure increased >2 mm Hg in all but 2 patients in group B during exercise. The mitral valve area did not change significantly during exercise in either group. The diastolic filling period decreased significantly and equally in both groups during exercise ($p < 0.001$).

Postoperatively, the changes in heart rate and LV peak systolic pressure were equal to preoperative changes during exercise in both groups. The LV end-diastolic pressure did not change in group A and increased from 12 ± 5 to 17 ± 4 mm Hg ($p < 0.02$) in group B during exercise after surgery. The mean mitral valve pressure gradient at rest decreased significantly after surgery in both groups ($p < 0.001$). None of the patients had significant residual stenosis or restenosis after surgery.

Pre- and postoperative angiographic data: A summary of the preoperative angiographic data is presented in Table II. The end-diastolic volume index did not change in either group during exercise; the end-systolic volume index increased significantly in group B and did not change in group A. The ejection fraction and stroke volume did not change in group A and decreased significantly in group B, while the peak systolic

pressure/end-systolic volume index ratio increased in group A and did not change in group B during exercise. Three of 6 patients with angina pectoris (all in group B) had significant coronary stenosis in one or more coronary vessels on coronary angiography. None of these patients underwent mitral valve surgery.

None of the resting angiographic values changed significantly after surgery in either group. The changes in LV volumes and ejection fraction during exercise postoperatively were equal to those during preoperative exercise testing in both groups.

Correlation of the change in mitral valve pressure gradient during exercise with other hemodynamic and angiographic data: The change in mitral pressure gradient during exercise did not correlate with any of the resting hemodynamic or angiographic data or with the changes in heart rate, LV peak systolic pressure, diastolic filling period or LV end-diastolic volume during exercise. A correlation did exist between the change in mitral pressure gradient during exercise and changes in ejection fraction ($r = 0.78$, $p < 0.001$) (Fig. 1), end-systolic volume index ($r = 0.69$, $p < 0.001$), peak systolic pressure/end-systolic volume ratio ($r = 0.61$, $p < 0.001$) and LV end-diastolic pressure ($r = 0.73$, $p < 0.001$).

Pre- and postoperative clinical data: The individual pre- and postoperative functional class of the patients is presented in Figure 2. All patients in group A showed symptomatic improvement after operation. In group B, 2 patients remained in class III and 3 were in class II postoperatively. Figure 3 presents the change in the maximal work load tolerated in bicycle ergometry. The maximal work load increased from 66 ± 20 to 94 ± 28 W ($p < 0.001$) in group A and did not change in group B (58 ± 26 W preoperatively and 55 ± 5 W postoperatively, difference not significant) after surgery.

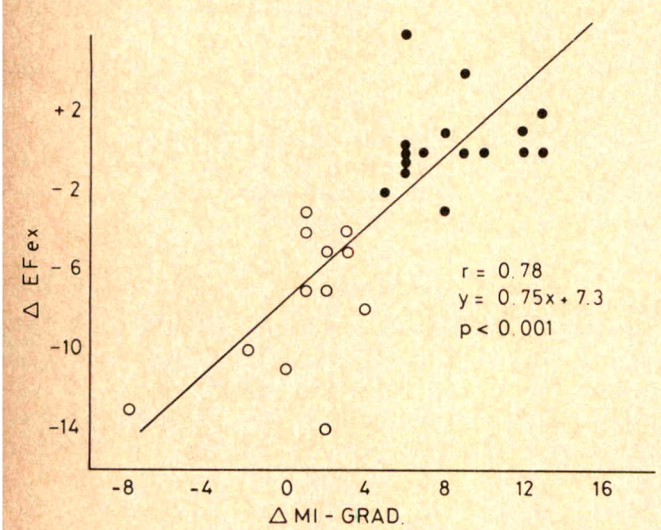

FIGURE 1. Correlation between the change in ejection fraction (EFex) (percent) and the change in mean mitral valve pressure gradient (MI–GRAD) (mm Hg) during isometric exercise. **Open dots** represent the patients in group B and **closed dots** patients in group A.

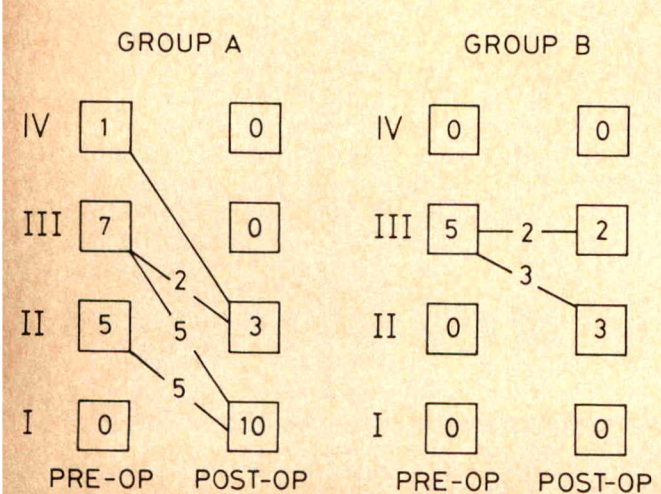

FIGURE 2. Individual changes in the New York Heart Association functional class after mitral valve surgery in groups A and B.

Discussion

Response to isometric exercise in mitral stenosis: Isometric exercise has been used to evaluate LV functional reserve in various cardiovascular disorders.[1–4] Isometric exercise induces a relatively modest increase in heart rate compared with dynamic exercise,[8] and therefore may offer a better means of evaluating the LV response to exercise in MS without excessive complications from a rate-related increase in inhibition of LV filling. The normal response to isometric exercise is a maintenance of ejection fraction and an increase of peak systolic pressure/end-systolic volume ratio.[9,10] More than a half of our patients showed a similiar response to handgrip exercise, indicating a normal response to stress. In 12 patients the ejection fraction decreased during exercise, suggesting impaired myocardial contractile reserves. The change in mitral valve pressure gradient during exercise correlated well with the changes in ventricular function. The increase of LV end-diastolic pressure reflected also the reduced re-

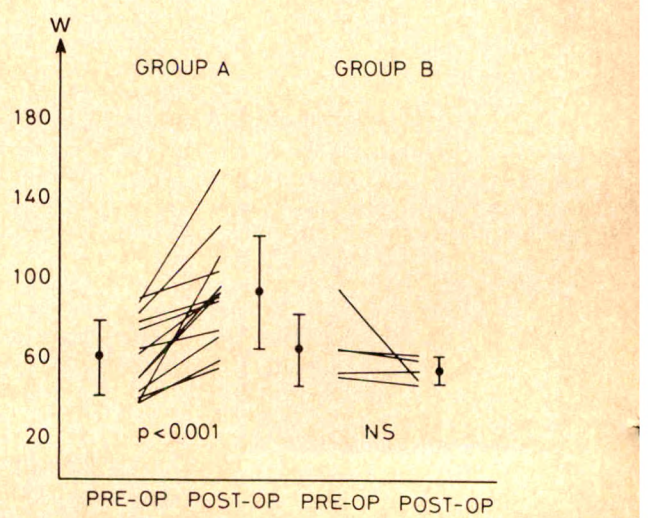

FIGURE 3. Individual values in the maximal work load tolerated in bicycle ergometry before and after mitral valve surgery in groups A and B.

sponse to exercise. However, in 2 patients the LV end-diastolic pressure did not increase despite the decrease in ejection fraction.

The increase in LV diastolic pressure without a significant increase in left atrial pressure may explain why the pressure gradient did not increase in some patients. Previously, the deterioration in LV ejection fraction in response to isometric exercise has been shown to be related to LV asynergy and stiffness.[9] Horwitz et al[11] demonstrated that patients with MS whose LV response to isometric exercise is reduced show posterobasal wall motion abnormalities in cineangiography. Contraction abnormalities, generally in the posterobasal area, also correlate well with abnormal LV response to afterload stress induced by angiotensin in MS.[12] Ischemic wall motion abnormalities due to coronary artery disease might well explain the reduced response to exercise. Two patients in group B had normal coronary arteriography and half of the patients in group B had no symptoms of angina pectoris; therefore, rigidity of posterobasal area of the left ventricle may explain the reduced LV response to isometric exercise.

Value of isometric exercise testing in predicting the postoperative outcome: LV dysfunction is a commonly suspected cause of poor surgical results in patients treated by either commissurotomy or valve replacement.[13–15] Our data are consistent with these findings; that is, the patients whose LV response to exercise was impaired preoperatively continued to have a reduced LV response to stress after surgery and their functional improvement was minimal. According to these findings, the mechanical obstruction imposed by the diseased mitral valve may not be the sole basis for the diminished exercise tolerance. Some of the symptoms experienced by the patients with MS may also be the result of impaired LV function. In such cases, surgical dilatation of the mitral valve cannot bring about the expected functional improvement.

The indications for surgery in MS are generally based on the symptomatic severity and degree of valvular lesion. Selzer[16] reported many patients with MS for whom careful clinical evaluation appeared to justify placement in functional class III, but whose cardiac catheterization revealed only trivial mitral valve obstruction. Although commissurotomy is a safe procedure, valve replacement still carries some risk of mortality and the valve prosthesis in the mitral position presents a modest risk of postoperative complications. To avoid unnecessary surgical interventions, more objective data may thus be needed when evaluating the indications for surgery, especially when a discrepancy exists between functional impairment and the degree of valvular obstruction. If cardiac catheterization is needed because of this discrepancy or for other reasons,[17] measurement of the mitral valve pressure gradient during isometric handgrip exercise, which can be performed quite safely and easily in our experience, might give some valuable information to assist in such therapeutic decisions.

Possible methodologic limitations: The variations in cycle length that occur with atrial fibrillation may affect the mitral valve pressure gradient. The diastolic filling period did not differ significantly between the groups either at rest or during exercise; therefore, the cycle length variation was probably not of major significance in the responses in the valvular pressure gradients during exercise in groups A and B. Also, coronary angiography was not performed in patients without angina pectoris. Significant coronary artery disease that is not clinically suspected has not been shown to be common in patients with MS.[18]

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Influence of Verapamil Therapy on Left Ventricular Performance at Rest and During Exercise in Hypertrophic Cardiomyopathy

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To determine the hemodynamic effect of verapamil at rest and during exercise, 18 patients with hypertrophic cardiomyopathy were studied before and after 7 weeks of treatment with oral verapamil (maximal dose, 720 mg/day). At rest and at peak exercise, verapamil produced a significant increase in left ventricular (LV) systolic performance in terms of stroke volume index (rest, from 43 ± 11 to 53 ± 11 ml/m^2, p <0.001; exercise, from 46 ± 11 to 51 ± 10 ml/m^2, p <0.01), whereas heart rate decreased (rest, from 81 ± 14 to 70 ± 11 min^{-1}, p <0.001; exercise, from 150 ± 21 to 141 ± 18 min^{-1}, p <0.01). Cardiac index at rest and during exercise remained unchanged. Systolic vascular resistance did not change at rest, but decreased significantly during exercise (974 ± 243 to 874 ± 174 dynes s cm^{-5}; p <0.05). After verapamil administration, pulmonary artery pressures did not change at rest, but decreased significantly during exercise. This was probably due to a shift in the LV pressure-volume relation. The improvement in LV hemodynamics was associated with a significant increase in exercise capacity. The findings of this study indicate that in patients with hypertrophic cardiomyopathy, hemodynamic improvement at rest and during exercise can be achieved by chronic administration of verapamil.

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Recently, several investigators have described the effectiveness of the slow calcium channel-blocking agent verapamil in the treatment of hypertrophic cardiomyopathy, although the exact mode of action of the drug in this specific disease is still unclear.[1–8] These studies report a beneficial effect of verapamil on symptoms, exercise capacity and left ventricular (LV) hemodynamics. Acute or chronic administration of verapamil results in a reduction of the LV pressure gradient and in an improvement of LV diastolic performance at rest.[5,7,8–12] However, no data are available on the hemodynamic effect of this drug on LV function during exercise. This study evaluates the effect of chronic high-dose verapamil administration on LV performance at rest and during exercise in patients with hypertrophic cardiomyopathy.

Methods

Patients: Eighteen patients, 4 men and 4 women, aged 25 to 58 years (mean 45 ± 10), participated in the study. In all patients the diagnosis of hypertrophic cardiomyopathy was based on clinical examination, echocardiographic study and on right- and left-sided cardiac catheterization. The echocardiographic criterion for hypertrophic cardiomyopathy was a disproportionate thickening of the ventricular septum with respect to the LV free wall (septal–LV free wall thickness ratio ≥1.5) in the absence of other acquired or congenital heart diseases. Coronary artery disease was excluded by selective coronary angiography. Six patients (5 men and 1 woman) had nonobstructive hypertrophic cardiomyopathy and 12 (9 men and 3 women) had an obstructive form with an LV pressure gradient either at rest or after provocation (postextrasystolic or amyl nitrite–induced gradient ≥30 mm Hg). The mean resting gradient was 53 ± 21 mm Hg (range 30 to 90) and the mean gradient at provocation was 95 ± 49 mm Hg (range 30 to 175) (Table I). All patients except 1 with atrial fibrillation (Case 16) had sinus rhythm. Three patients had angiographically proved mitral regurgitation. In 2 of the 3 (Cases 7 and 8), it was mild (Class I); in the third (Case 16), it was severe (Class III).

LV exercise hemodynamics were measured with a Swan-Ganz thermodilution catheter advanced to the pulmonary artery. Cardiac output was measured in triplicate by thermodilution. Pulmonary artery pressure measurements were based on the analysis of 5 consecutive cycles.

Arterial blood pressure was measured with cuff manometer. Exercise was performed on a braked bicycle ergometer with the patient in the supine position. Initial work load was 50 W; it increased progressively by 25 W at 3-minute intervals, while patients maintained a constant pedaling rate of 40 rpm.

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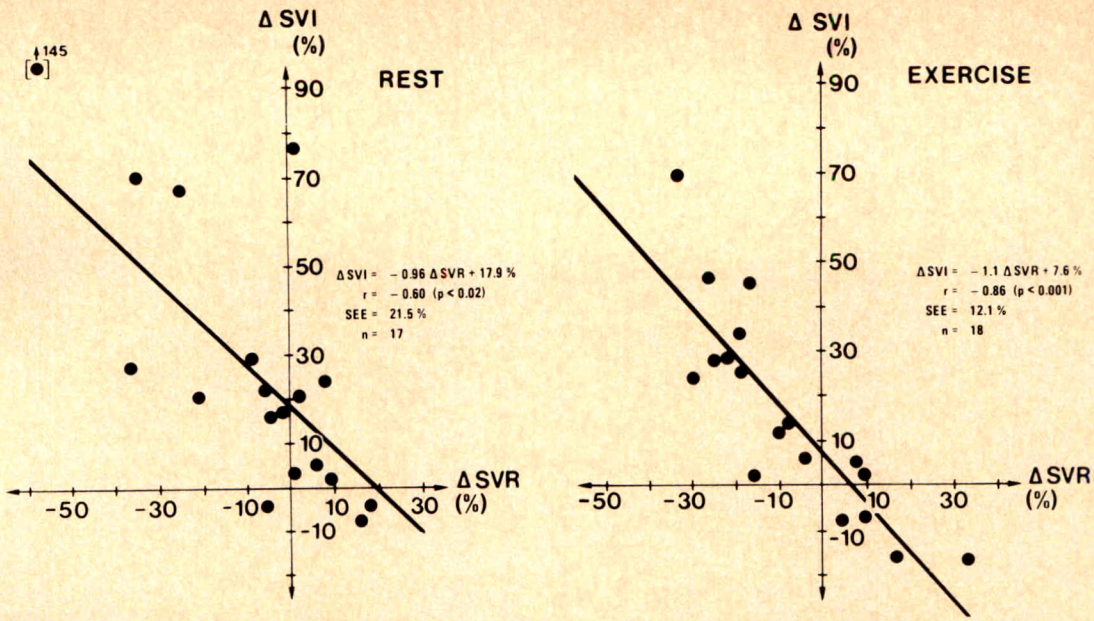

FIGURE 1. Correlation between percent change in systemic vascular resistance (ΔSVR) and percent change in stroke volume index (ΔSVI) at rest (**left panel**) and at peak exercise (**right panel**) after verapamil treatment. The **black circle in brackets** in the **left panel** was excluded from the regression calculations. SEE = standard error of the estimate.

Maximal work rate in the individual patient was calculated by summing the work rate in kpm/min (W) of each exercise step achieved.[13]

Hemodynamic measurements were taken at rest and at maximal exercise. Exercise was performed until angina, limiting fatigue or dyspnea developed. In patients who had angina, exercise was continued until angina caused them to stop. In 1 patient (Case 6), exercise was discontinued because of severe arrhythmia (Lown grade 4B). In Cases 6 and 8, control pulmonary artery pressures could not be determined at rest or during exercise for technical reasons.

All medication was stopped at least 3 days before the hemodynamic control measurement was performed. Thereafter, each patient received 40 mg of verapamil 3 times/day. Within the next 6 weeks the dosage was slowly increased in 17 patients to a maximal dosage of 120 mg 6 times/day. One patient (Case 15) received a maximum of 120 mg 4 times/day. After an average treatment of 7 weeks (range 4 to 12) with maximal verapamil dosage, repeat hemodynamic measurements at rest and during maximal exercise were performed in each patient. The examination was performed 2 hours after the morning dose. No serious adverse effects relating to the large verapamil dosage[14] and complications related to the investigations were observed.

Calculations and statistical analysis: Cardiac index (CI, liters/min/m^2) was calculated as cardiac output (CO)/body surface area. Stroke volume index (ml/m^2) was calculated as CI/heart rate. Pulmonary vascular resistance (dynes s cm^{-5}) was calculated as (MPAP − EDPAP)/CO × 80, where MPAP = mean pulmonary artery pressure and EDPAP = end-diastolic pulmonary artery pressure. Systemic vascular resistance (dynes s cm^{-5}) was calculated as ($\overline{AP}$/CO) × 80, where $\overline{AP}$ = mean arterial pressure. (Mean arterial pressure was estimated from the formula AP = SP + 2 DP/3, where SP = peak systolic and DP = diastolic blood pressure.[15] In the patient with atrial fibrillation, the mean AP was determined from several consecutive readings.)

Results are expressed as mean values ±1 standard deviation. A Student *t* test for paired comparison was used to compare values before and after treatment. Differences were regarded as significant at $p < 0.05$.

Results

Individual and mean values of the hemodynamic measurements at rest and at peak exercise before and after chronic verapamil therapy are listed in Table I. On an average, the maximal work rate improved significantly from initially 626 ± 296 to 779 ± 363 W after verapamil therapy ($p < 0.01$). Compared with control measurements, the stroke volume index increased significantly at rest and during exercise (rest, from 43 ± 11 to 53 ± 11 ml/m^2, $p < 0.001$; exercise, from 46 ± 11 to 51 ± 10 ml/m^2, $p < 0.01$), whereas resting and exercise heart rate decreased from 81 ± 14 min^{-1} to 70 ± 11 min^{-1} ($p < 0.001$) and from 150 ± 21 min^{-1} to 141 ± 18 min^{-1} ($p < 0.01$), respectively. Consequently, cardiac index did not change (rest, from 3.5 ± 0.7 to 3.7 ± 0.9 liters/min/m^2, difference not significant [NS]; exercise, from 6.7 ± 1.4 to 7.2 ± 1.2 liters/min/m^2, NS).

The mean arterial blood pressure decreased significantly (rest, from 107 ± 9 to 102 ± 10 mm Hg, $p < 0.05$; exercise, from 145 ± 15 to 140 ± 16 mm Hg, $p < 0.05$), as did systemic vascular resistance during exercise (974 ± 243 to 874 ± 174 dynes s cm^{-5}, $p < 0.05$). Significant negative correlations were found at rest and at maximal exercise between the percent changes in systemic vascular resistance and stroke volume index (Fig. 1). Pulmonary vascular resistance remained unchanged.

Pulmonary artery pressures, on an average, did not change at rest. During exercise, a significant decrease in pulmonary artery pressures was observed. Systolic pulmonary artery pressure at maximal exercise decreased from 61 ± 18 mm Hg before to 51 ± 13 mm Hg after verapamil therapy ($p < 0.01$), while mean and end-diastolic pulmonary artery pressures decreased from 43 ± 15 to 37 ± 10 mm Hg ($p < 0.02$) and from 32 ± 11 to 24 ± 7 mm Hg ($p < 0.001$), respectively.

A general decrease in pulmonary artery pressures during exercise was observed in 12 patients. In 2 more

TABLE I Hemodynamic Parameters at Rest and at Peak Exercise Before and After Long-Term Verapamil Therapy

Case	Age (yr) & Sex	ΔP		HR (min^{-1}) R	HR (min^{-1}) E	MAP (mm Hg) R	MAP (mm Hg) E	SVR (dynes s cm^{-5}) R	SVR (dynes s cm^{-5}) E	SVI (ml/m^2) R	SVI (ml/m^2)
1	25M	∅	C	55	170	97	157	1218	1023	59	
			V	50	144	90	145	1227	828	61	
2	58M	∅	C	82	118	100	125	1272	870	34	
			V	83	120	107	122	1159	908	44	
3	40M	∅	C	85	155	108	130	1585	843	38	
			V	75	150	102	142	1846	1125	35	
4	54M	∅	C	80	125	110	143	1408	1309	36	
			V	68	128	105	130	1377	920	42	
5	37M	∅	C	92	148	107	153	965	847	51	
			V	85	134	110	140	919	688	59	
6	55F	∅	C	113	175	120	137	2909	1363	20	
			V	87	138	97	130	1232	1134	49	
7	44M	R 36	C	68	122	113	140	1326	878	59	
			V	56	126	103	143	1451	1025	60	
8	43M	R 50	C	75	144	107	127	1518	742	39	
			V	73	135	98	122	1197	711	47	
9	30F	R 30	C	105	160	93	123	1465	1643	30	
			V	70	142	93	120	1479	1092	53	
10	52M	R 60	C	86	160	115	163	1418	887	43	
			V	65	155	107	167	1058	973	72	
11	38M	R 50	C	93	150	117	155	836	630	54	
			V	75	130	107	153	785	679	66	
12	55M	R 90	C	85	134	90	137	1076	840	38	
			V	68	145	95	130	1164	707	47	
13	57M	P 175	C	65	115	123	157	1400	921	54	
			V	58	114	135	158	1430	829	65	
14	40M	P 75	C	70	175	103	177	1268	970	48	
			V	63	175	105	168	1500	728	46	
15	50F	P 120	C	67	145	110	143	1555	1057	50	
			V	72	128	107	133	1471	981	48	
16	42M	P 80	C	75	180	97	127	1805	904	30	
			V	62	165	90	117	1180	670	51	
17	48M	P 90	C	75	145	100	160	1013	827	55	
			V	86	130	93	145	641	647	70	
18	41F	P 30	C	90	175	110	153	1464	983	40	
			V	71	180	97	160	1548	1078	42	
Mean value ± 1 SD			C	81 ± 14	150 ± 21	107 ± 9	145 ± 15	1417 ± 444	974 ± 243	43 ± 11	46 ±
Mean value ± 1 SD			V	70 ± 11	141 ± 18	102 ± 10	140 ± 16	1259 ± 292	874 ± 174	53 ± 11	51 ±
			C vs V	p <0.001	p <0.01	p <0.05	p <0.05	NS	p <0.05	p <0.001	p <(

C = control; CI = cardiac index; E = exercise; EDPAP = end-diastolic pulmonary artery pressure; HR = heart rate; MAP = mean artery press
Max. = maximal; MPAP = mean pulmonary artery pressure; NS = not significant; P = provocation; ΔP = left ventricular outflow gradient;

(Cases 5 and 18), only end-diastolic pressure decreased, whereas systolic and mean pulmonary artery pressures either increased or the former remained constant and the latter increased. One patient (Case 14) had no change in end-diastolic pulmonary artery pressure (but had increased systolic and mean pressures); another patient (Case 17) had increased end-diastolic pulmonary artery pressure (with no change in systolic and mean pressures). However, the decrease in end-diastolic pulmonary artery pressure observed at maximal exercise in these 14 patients was associated with an improvement in stroke volume index of at least 5% in only 8 patients; no change occurred in 2 (Cases 10 and 12) and a deterioration in stroke volume index was seen in 4 (Cases 2, 3, 7 and 18). Stroke volume also improved in the 2 patients in whom no control measurements were available (Cases 6 and 8) and in the 2 with unchanged or increased end-diastolic pulmonary artery pressure (Cases 14 and 17).

Figure 2 illustrates the general relation between end-diastolic pulmonary artery pressure and stroke volume index in our study group. The mean values (±SD) are shown for each measurement at rest and at maximal exercise for the control and the verapa state. At rest, chronic verapamil treatment does change end-diastolic pulmonary artery pressure, w stroke volume is significantly increased. During exerc stroke volume index does not change significantly eit before or after verapamil treatment. At maximal ex cise, however, end-diastolic pulmonary artery press is significantly reduced after administration of ve pamil and stroke volume index is still significantly creased. Thus, on an average, there is an upward a leftward shift of the patient's hemodynamic exerc status after verapamil therapy, indicating impro cardiac performance.

In the small group of patients studied, there was obvious difference in the hemodynamic behavior at r and with exercise between the obstructive and nonobstructive form of hypertrophic cardiomy athy.

Discussion

The present data show that chronic verapamil th apy in patients with hypertrophic cardiomyopathy l a beneficial effect on LV hemodynamics at rest a

ABLE I, continued

CI (l/min·m²)		SPAP (mm Hg)		MPAP (mm Hg)		EDPAP (mm Hg)		PVR (dynes s cm⁻⁵)		Max Work Rate (W)
R	E	R	E	R	E	R	E	R	E	
3.3	6.4	16	44	8	22	3	16	63	39	750
3.1	7.3	18	28	12	18	5	14	95	23	1050
3.6	6.1	38	72	25	54	18	37	83	118	375
3.7	5.7	47	69	29	50	19	32	116	137	450
3.3	7.4	34	63	25	48	16	33	132	97	525
2.7	6.1	26	41	18	29	12	20	109	71	450
2.9	4.1	35	85	25	68	20	45	64	210	1100
2.8	5.3	27	54	20	43	12	28	105	106	850
4.7	7.6	26	44	15	28	11	20	36	44	750
5.0	8.6	33	48	22	35	13	18	75	83	1000
2.2	5.4	33	. . .	21	. . .	14	. . .	170	. . .	100
4.3	6.2	33	48	19	22	8	11	140	96	225
4.0	7.5	23	47	18	36	10	28	94	50	550
3.4	6.6	40	44	25	35	18	26	99	64	850
2.9	7.1	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	550
3.4	7.1	32	72	20	59	16	49	49	58	750
3.2	3.7	59	100	43	72	35	58	126	187	125
3.1	5.5	59	84	40	60	23	40	270	182	200
3.7	8.4	17	45	10	35	5	21	62	76	950
4.7	7.9	14	38	8	29	5	16	30	76	900
5.0	8.9	30	75	18	45	15	48	21	12	800
4.9	8.1	30	53	22	36	15	33	51	13	1400
3.3	6.4	18	52	13	39	6	32	84	43	725
3.2	7.2	25	55	13	38	7	20	73	98	875
3.5	6.8	41	90	23	65	17	40	68	147	500
3.8	7.7	30	58	20	43	10	25	106	94	600
3.3	7.5	23	49	13	37	8	28	61	49	1050
2.9	9.5	31	63	18	40	10	28	114	52	1250
3.3	6.4	26	52	19	39	11	32	113	52	375
3.4	6.4	28	40	19	28	12	19	96	66	450
2.2	5.8	29	62	21	42	15	32	112	71	450
3.2	7.3	23	50	17	38	10	25	92	74	750
4.1	8.1	25	42	19	30	11	19	81	57	1050
6.0	9.3	21	43	15	31	8	22	48	40	1425
3.6	7.4	17	54	14	33	4	29	133	26	550
3.0	7.1	18	54	12	37	4	25	128	81	550
3.5 ± 0.7	6.7 ± 1.4	29 ± 11	61 ± 18	19 ± 8	43 ± 15	13 ± 8	32 ± 11	88 ± 38	80 ± 58	626 ± 296
3.7 ± 0.9	7.2 ± 1.2	30 ± 11	51 ± 13	19 ± 7	37 ± 10	11 ± 5	24 ± 7	103 ± 52	79 ± 41	779 ± 363
NS	NS	NS	p <0.01	NS	p <0.02	NS	p <0.001	NS	NS	p <0.01

= pulmonary vascular resistance; R = rest; SD = standard deviation; SPAP = systolic pulmonary artery pressure; SVI = stroke volume index; SVR = systemic vascular resistance; V = verapamil; ∅ = not available.

during exercise. LV systolic performance in terms of stroke volume index improved, on an average, by 23% at rest and by 12% at maximal exercise.

We believe that the main pharmacologic effects of chronic high-dose verapamil application responsible for the increase in stroke volume are the vasodilating action and the decrease in heart rate. Verapamil has been shown to have a systemic vasodilative effect[16,17] in patients with various types of heart disease. This finding is reflected in our study by the decreased mean arterial pressures. A significant reduction of systemic vascular resistance could only be documented during exercise, yet the significant negative correlations between the percent changes in systemic vascular resistance and stroke volume index at rest as well as during exercise (Fig. 1) strongly suggest that one of the causes for the improvement in systolic performance in our study group is the vasodilating effect of verapamil. A similar increase in stroke volume accompanied by a moderate decline in systemic resistance was also reported by Chatterjee et al.[11]

The heart rate at rest and during exercise was significantly reduced in our patient group. The reduction of heart rate in patients with hypertrophic cardiomyopathy who received verapamil therapy has been observed by other investigators[5,8,18] and probably reflects the depressing action of the drug on the sinus node automaticity when administered chronically. The reduced heart rate causes improved diastolic filling, which in turn improves stroke volume according to the Frank-Starling mechanism. As a consequence of decreased heart rate and increased stroke volume index, cardiac index remained constant.

Although cardiac output did not increase, most patients performed more exercise after verapamil therapy, as previously reported by Rosing et al.[5] Several factors may be considered responsible for the improved exercise capacity. The significant decrease in pulmonary artery pressures during exercise may have improved working capacity because of an amelioration of dyspnea. In addition, the decrease in end-diastolic pulmonary artery pressure—representing a decrease in LV end-diastolic pressure—may indicate reduced subendocardial ischemia during exercise secondary to decreased LV diastolic wall tension. Furthermore, heart rate, as one of the major determinants of myocardial oxygen con-

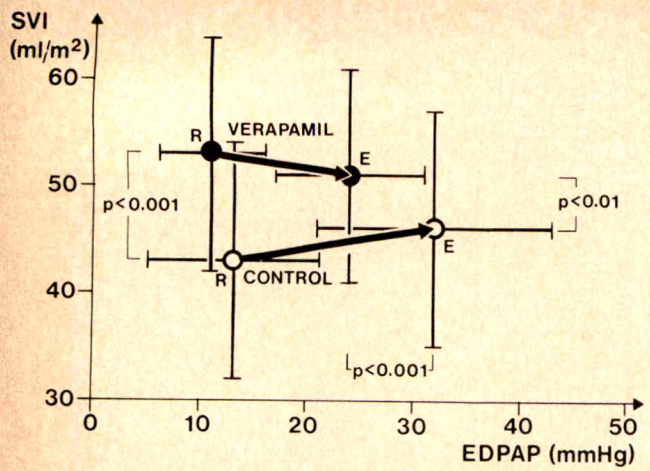

FIGURE 2. Mean values (±1 standard deviation) of end-diastolic pulmonary artery pressure (EDPAP) and stroke volume index (SVI) at rest (R) and at maximal exercise (E) in the same group of patients before (CONTROL) and after (VERAPAMIL) chronic treatment with verapamil. Verapamil significantly ($p < 0.001$) increased SVI at rest, while EDPAP remained constant. At exercise, in the verapamil group, SVI remained significantly increased ($p < 0.01$) with respect to the control group and EDPAP significantly decreased ($p < 0.001$). This reflects improved cardiac performance at rest and during exercise after verapamil. The p values were determined from paired *t* tests.

sumption, was significantly reduced during exercise after verapamil administration. In patients with obstructive hypertrophic cardiomyopathy, oral verapamil also diminished the pressure gradient,[3] further reducing myocardial oxygen demand.

Verapamil has been reported to have no venous pooling effect.[16,17] Although the present data do not explicitly exclude venous pooling (since right atrial pressures were not measured), the constant resting end-diastolic pulmonary artery pressure before and after verapamil administration suggests no change in the circulating blood volume. Other authors have made similar observations.[4,10,11] They also found that resting LV end-diastolic pressure remained unchanged after acute or chronic verapamil administration.

The mechanism underlying the reduction of pulmonary artery pressure during exercise after verapamil treatment is unclear. In patients with hypertrophic cardiomyopathy, several groups of investigators reported that verapamil causes an improvement in LV relaxation, as reflected in shortened isovolumic relaxation time, increased rate of LV filling or wall thinning, reduced LV end-diastolic pressure and a downward shift of the LV pressure-volume curve.[7,8,10–12] These alterations in diastolic function may be caused by myocardial ischemia. Despite normal extramural coronary arteries, stressed-induced ischemia has been documented in patients with hypertrophic cardiomyopathy by electrocardiographic stress testing, thallium scintigraphy and myocardial lactate sampling.[19] In these patients, ischemia was believed to be caused by narrowed intramural vessels[20] or by an imbalance in the oxygen supply-demand ratio.

The results of this study demonstrate that chronic oral verapamil administration can improve LV hemodynamics at rest and during exercise in many patients with hypertrophic cardiomyopathy. The mild adverse hemodynamic effects during verapamil therapy in individual patients were not accompanied by corresponding symptoms or clinical findings and in no case led to a withdrawal of verapamil.

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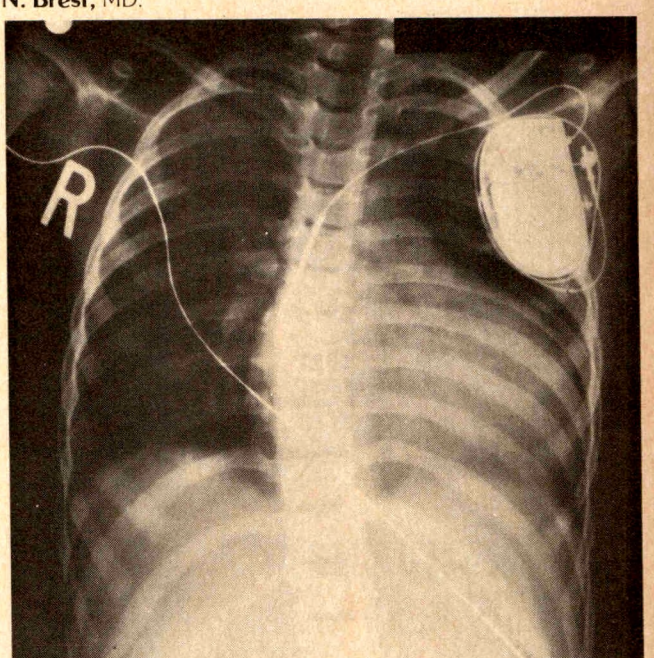

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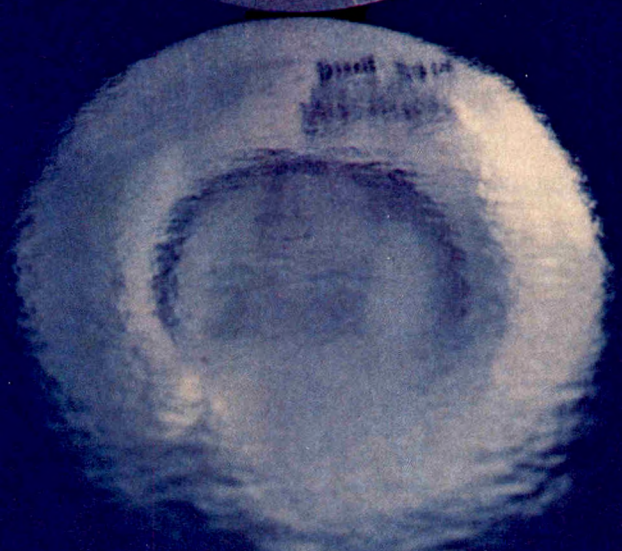

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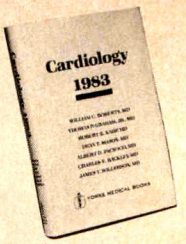

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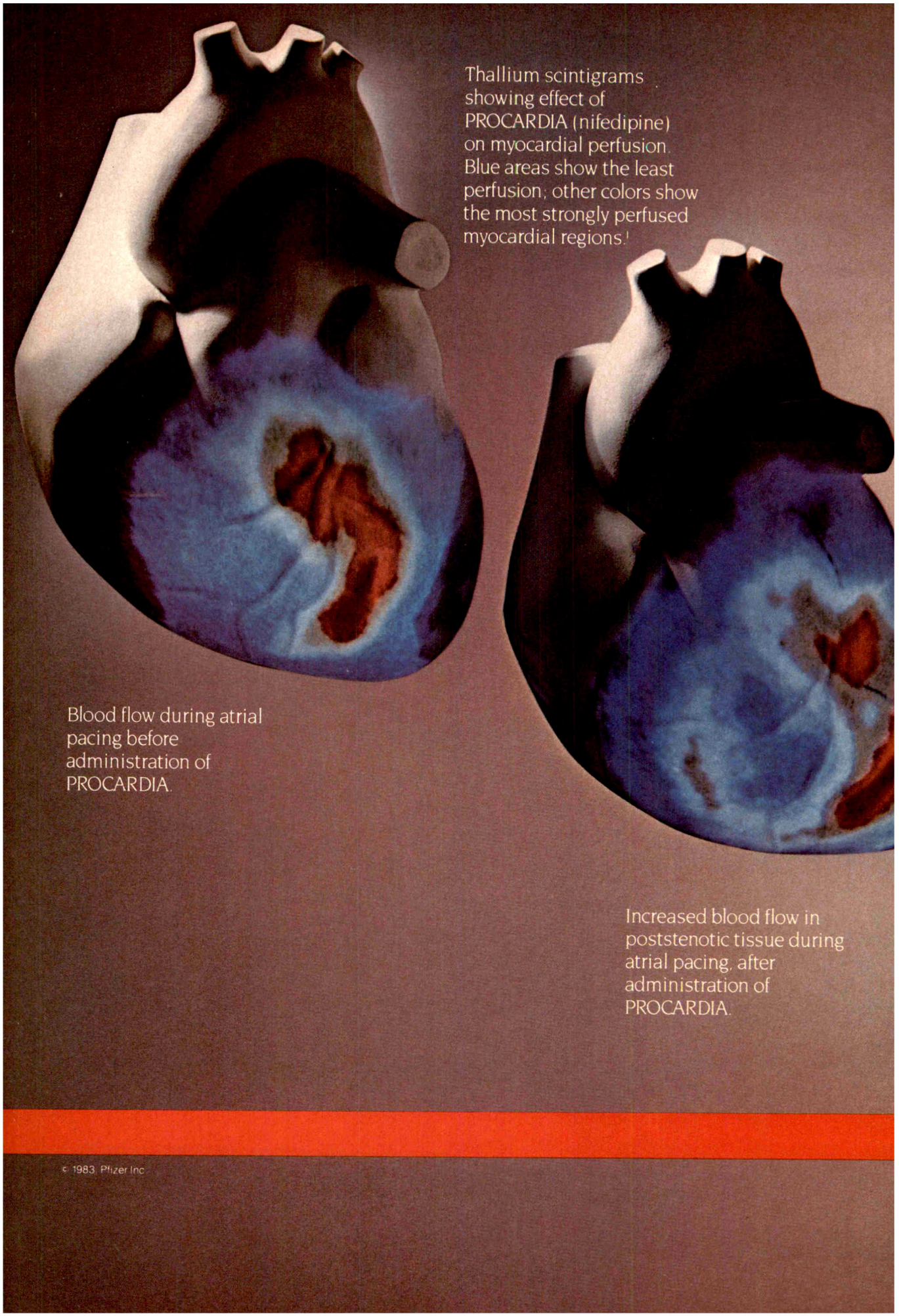

Thallium scintigrams showing effect of PROCARDIA (nifedipine) on myocardial perfusion. Blue areas show the least perfusion; other colors show the most strongly perfused myocardial regions.[1]

Blood flow during atrial pacing before administration of PROCARDIA.

Increased blood flow in poststenotic tissue during atrial pacing, after administration of PROCARDIA.

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Angina is caused by ischemia that results from atherosclerosis alone, vasoconstriction alone, or a combination of both. By preventing vasoconstriction, and increasing myocardial blood supply, Procardia may help limit angina* due to an inadequate supply of blood.

*Procardia is indicated for the management of:

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- Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina), Procardia has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete. In general, dilation of coronary arteries does not appear to be an important part of Procardia action in classical angina.

for the varied faces of angina.

1. Engel H-J, in Angina Pectoris: New Concepts—New Treatment, film, New York, Synthesis Communications, Inc. 1981.

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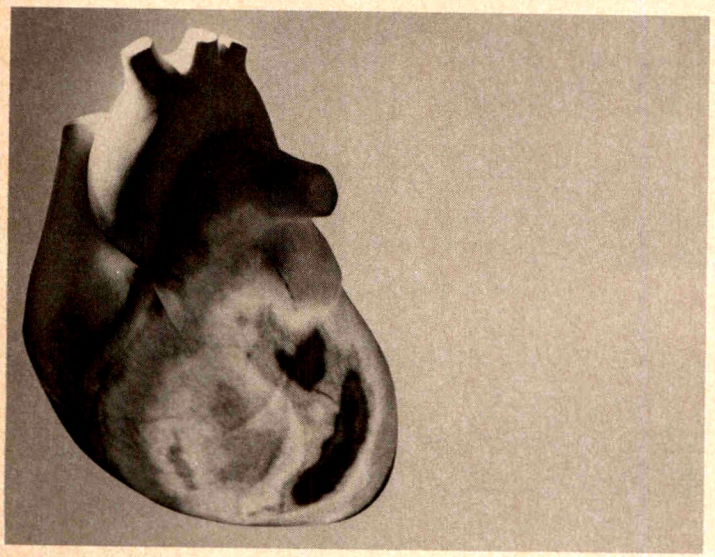
Please see PROCARDIA® *brief summary on next page.*

increasing myocardial blood flow



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–Usual effective dosage is 30-60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because Procardia decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration is suggested. Close observation is especially recommended for patients taking medication known to lower blood pressure.

–Offers a favorable safety profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

BRIEF SUMMARY
PROCARDIA* (nifedipine) **CAPSULES** F
INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is in
the management of vasospastic angina confirmed by any of the following criteria: 1
pattern of angina at rest accompanied by ST segment elevation, 2) angina or coror
spasm provoked by ergonovine, or 3) angiographically demonstrated coronary arte
In those patients who have had angiography, the presence of significant fixed obstr
ease is not incompatible with the diagnosis of vasospastic angina, provided that the
teria are satisfied. PROCARDIA may also be used where the clinical presentation
possible vasospastic component but where vasospasm has not been confirmed, e
pain has a variable threshold on exertion or in unstable angina where electrocardiogr
ings are compatible with intermittent vasospasm, or when angina is refractory to ni
or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA i
for the management of chronic stable angina (effort-associated angina) without e
vasospasm in patients who remain symptomatic despite adequate doses of beta blo
or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effect
trolled trials of up to eight weeks duration in reducing angina frequency and increasir
tolerance, but confirmation of sustained effectiveness and evaluation of long-terr
these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PF
and beta-blocking agents may be beneficial in patients with chronic stable angina, bu
information is not sufficient to predict with confidence the effects of concurrent trea
pecially in patients with compromised left ventricular function or cardiac conduction
ities. When introducing such concomitant therapy, care must be taken to mon
pressure closely since severe hypotension can occur from the combined effects of
(See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensiv
PROCARDIA is modest and well tolerated, occasional patients have had excessive
tolerated hypotension. These responses have usually occurred during initial titratio
time of subsequent upward dosage adjustment, and may be more likely in patients or
itant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been repor
tients receiving PROCARDIA together with a beta blocking agent who underwent co
tery bypass surgery using high dose fentanyl anesthesia. The interaction with
fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, bu
sibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in othe
procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA t
tients where surgery using high dose fentanyl anesthesia is contemplated, the physici
be aware of these potential problems and, if the patient's condition permits, sufficie
least 36 hours) should be allowed for PROCARDIA to be washed out of the boc
surgery.

Increased Angina: Occasional patients have developed well-documented incre
quency, duration or severity of angina on starting PROCARDIA or at the time of d
creases. The mechanism of this response is not established but could result from
coronary perfusion associated with decreased diastolic pressure with increased hea
from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may
withdrawal syndrome with increased angina, probably related to increased sensitivit
cholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and
expected to exacerbate it by provoking reflex catecholamine release. There have be
sional reports of increased angina in a setting of beta blocker withdrawal and PROCA
tiation. It is important to taper beta blockers if possible, rather than stoppi
abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have d
heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be
risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral
resistance, careful monitoring of blood pressure during the initial administration
tion of PROCARDIA is suggested. Close observation is especially recommended for
already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with ar
sodilation and not due to left ventricular dysfunction, occurs in about one in ten patient
with PROCARDIA. This edema occurs primarily in the lower extremities and usually
to diuretic therapy. With patients whose angina is complicated by congestive heart fai
should be taken to differentiate this peripheral edema from the effects of increasing le
ular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warning
rience in over 1400 patients in a non-comparative clinical trial has shown that con
administration of PROCARDIA and beta-blocking agents is usually well tolerated.
have been occasional literature reports suggesting that the combination may increase
lihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates,
have been no controlled studies to evaluate the antianginal effectiveness of this comb

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels i
twelve normal volunteers. The average increase was 45%. Another investigator fou
crease in digoxin levels in thirteen patients with coronary artery disease. In an unc
study of over two hundred patients with congestive heart failure during which digoxin b
els were not measured, digitalis toxicity was not observed. Since there have been iso
ports of patients with elevated digoxin levels, it is recommended that digoxin l
monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible
under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to ma
fedipine caused reduced fertility at a dose approximately 30 times the maximum recom
human dose.

Pregnancy: Category C. Please see full prescribing information with reference to terato
in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-
ness, peripheral edema, nausea, weakness, headache and flushing each occurring
10% of patients, transient hypotension in about 5%, palpitation in about 2% and sy
about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA
comitant antianginal medication. Additionally, the following have been reported:
cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation,
mation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in
dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rare
duction of PROCARDIA therapy was associated with an increase in anginal pain, poss
to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable
natural history of the disease in these patients. It remains possible, however, that
many of these events were drug related. Myocardial infarction occurred in about 4% of
and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias
duction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as
phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident o
cantly elevated transaminases and alkaline phosphatase was seen in a patient with a h
gall bladder disease after about eleven months of nifedipine therapy. The relation
PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been as
with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been
twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg o
pine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 3
0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should
tected from light and moisture and stored at controlled room temperature 59° to 77°F
25°C) in the manufacturer's original container.

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Changing Results and Concepts in the Surgical Treatment of Double-Outlet Right Ventricle: Analysis of 137 Operations in 126 Patients

GIAN PICCOLI, MD, ALBERT D. PACIFICO, MD, JOHN W. KIRKLIN, MD, EUGENE H. BLACKSTONE, MD, JAMES K. KIRKLIN, MD, and LIONEL M. BARGERON, Jr., MD

One hundred thirty-seven operations (98 repairs and 39 preliminary or palliative operations) were performed for double-outlet right ventricle (DORV) with concordant atrioventricular connection from January 1967 through July 1982, with 36 hospital deaths (26%). Sixteen (12% of the total of 137 operations) of the nonrepair operations were palliative for uncorrectable malformations.

"Classic" DORV was palliated rather than repaired only when there was severe left ventricular or mitral hypoplasia or both (n = 4). Incremental risk factors for hospital death after repair of this subset for the entire period (n = 42) included young age at operation, type of repair and the era. In the current era (1978 through July 1982), 1 death (5%; 70% confidence limits 0.7 to 17%) occurred among 19 patients; the incremental risk for young age was evident only in patients <3 months old. Eleven deaths (39%) occurred among 28 patients who underwent repair of the Taussig-Bing type of DORV, with no decrease in mortality rate in the current era. Inclusion of a venous switch in the repair was the only incremental risk factor. Twenty-four patients with more-or-less normally positioned great arteries or with D-malposition but with noncommitted VSDs or complete atrioventricular canal defects underwent repair, with 7 hospital deaths; only 1 death occurred in the 11 operated upon in the current era. Four patients with DORV and L-malposition underwent repair, with no deaths. Three patients with superior-inferior ventricles and inlet VSD were considered uncorrectable and received successful palliative procedures.

Thus, results of repair in the current era are good in all subsets, even in infants, except for the Taussig-Bing heart. For this condition, a repair that does not include a venous switch is recommended. (Am J Cardiol 1983;52:549–554)

Many reports concerning the repair of double-outlet right ventricle (DORV) have failed to classify accurately the morphology of the malformation in the patients treated and the relation of this to the risks of the operation. Little cognizance has been taken in the surgical literature of the fact that some kinds of DORV are not amenable to repair and must be managed by other techniques. The results of repairs done by current techniques, including the use of cold cardioplegia, have not been separated from those of earlier periods.

From the Departments of Surgery and Pediatrics, School of Medicine and the Medical Center, The University of Alabama in Birmingham, and the Alabama Congenital Heart Disease Diagnosis and Treatment Center, Birmingham, Alabama. Manuscript received January 31, 1983; revised manuscript received May 12, 1983, accepted May 16, 1983.

Address for reprints: John W. Kirklin, M.D., Department of Surgery, University Station, Birmingham, Alabama 35294.

To define the current risks and residual problems of repair, we reviewed and analyzed our surgical experience with DORV with concordant atrioventricular connection to provide this kind of information.

Methods

Definition: For this study, we define DORV as a condition in which both great arteries arise wholly or nearly so from the morphologic right ventricle. The study includes only patients with atrioventricular concordant connection. Patients with situs ambiguus were tabulated but excluded from the analysis.

A few special situations require comment: (1) Tetralogy of Fallot is a morphologic spectrum that includes a variable amount of dextroposition of the aorta. In some cases the aorta arises >50% from the right ventricle. In this study, the malformation was considered DORV only when the aorta arose almost entirely (≥90%) from the right ventricle. (2) The

Taussig-Bing malformation (as described below) is also an entity with a spectrum, including biventricular origin of the pulmonary artery. This malformation has been considered under the heading of DORV unless the pulmonary artery arises wholly or nearly so (≥90%) from the left ventricle; then it is considered to be transposition of the great arteries with ventricular septal defect (VSD). (3) Some hearts with an anterior VSD in the outlet portion of the ventricular septum have both great arteries arising over the VSD. If >50% of both great arteries originate from left ventricle, the condition is termed double-outlet left ventricle; if both great arteries arise >50% from right ventricle, it is called DORV and is included in the study.

Material: All cases of DORV of the type described in which a cardiac surgical procedure was carried out between January 1967 and July 1982 are included in this review. All information available in the clinical records, the operative notes and, where available, autopsy reports, has been reviewed, as well as the cineangiograms from cases of uncertain morphology. Cases have been recategorized, where necessary, according to current morphologic concepts.

Morphologic categorization: The morphologic categorization is based primarily on a description of the position and interrelationships of the great arteries, and the location of the VSD in the ventricular septum and its relationship to the great arteries and the atrioventricular valves.[1,2] The great arteries were considered to be in 1 of 3 positions: (1) more-or-less normally positioned and interrelated; (2) the aorta anterior, either directly or a little to the right (the position of the great arteries in most patients with ordinary transposition of the great arteries), so-called D-malposition of the aorta; (3) the aorta to the left and side by side with the pulmonary artery. In the last 2 categories, the ascending aorta and pulmonary or trunk are parallel, whereas in the first category they are generally crossing.

The VSD as viewed from the right ventricular side is considered to be *perimembranous* when it abuts the anulus of the tricuspid valve.[3] It is categorized as being in the outlet portion of the septum when it is anterosuperior in location. It is categorized as being *trabecular* or inlet in position when it is that portion of the septum. Inlet VSD may be perimembranous (atrioventricular canal–type of VSD) or muscular. In a few cases, the VSD was part of a complete atrioventricular canal defect. Multiple VSDs were noted when present.

The VSD was further described in terms of its relation to the great arteries. It was considered to be closely related to the aortic origin (*subaortic*), closely related to the pulmonary origin (*subpulmonary*) or closely related to neither (*non-committed*).[1] Some subaortic VSDs extended anterosuperiorly and were closely related to the pulmonary artery as well, and were considered to be *doubly committed.*

Classic DORV is defined as an entity in which the great arteries are more or less normally interrelated, the VSD is perimembranous or nearly so in position and is subaortic or doubly committed. The *Taussig-Bing heart* is a form of DORV in which the aorta is anterior, sometimes to the right and sometimes to the left, and the great arteries are parallel and in the position usually found in ordinary transposition. The aortic and pulmonary valves are separated by the displaced infundibular septum, which is not interventricular. The VSD is located anterosuperiorly in the septum and is subpulmonary. Cases are accepted in which the pulmonary artery straddles the VSD and is biventricular in origin (see above).

In some patients with DORV and atrioventricular concordance, the position of the ventricles is abnormal. In cases in this study with this rotational anomaly, termed *superior-inferior ventricle*, the viscera and atria were in situs solitus, and the left ventricle was inferior and slightly posterior to the right ventricle, which was superior. An inherent part of this entity is a VSD that is in the inlet portion of the septum. In 2 of the 3 patients with this subset of DORV, a ventricular L-loop was present, yet the atrioventricular connection was concordant (criss-cross[4]). The aorta was to the left in 2 of the 3 cases. All also had pulmonary stenosis.

Analytical methods: The data were examined in simple contingency tables, and chi-square and Fisher's tests of significance were applied. Continuous variables were compared by the Student *t* test.

The incremental risk factors for hospital death were determined by logistic multivariate regression analysis for the classic and Taussig-Bing groups.[5] For the classic group, the variables examined were age, sex, ratio of right versus left ventricular enlargement, right ventricular outflow obstruction (yes or no), peripheral pulmonary artery stenosis (yes or no), restrictive (in size) versus nonrestrictive VSD, presence or absence of major associated cardiac anomalies, previous palliative operations, date of operation, cardioplegia (yes or no), atrial versus ventricular approach for the repair, surgical enlargement of the VSD (yes or no), and simple repair (which included cases in which an outflow patch limited to the right ventricular infundibulum was used) versus transanular patching versus valved extracardiac conduit. The analysis was performed for 41 patients. For the Taussig-Bing group, the same variables were examined plus presence or absence of a "venous switch" operation (Mustard or Senning repair).

TABLE I Repair of Double-Outlet Right Ventricle at The University of Alabama in Birmingham From January 1967 Through July 1982 (n = 98*)

	1967–1978			1978–July 1982		
		Hospital Deaths			Hospital Deaths	
Category†	No.	No.	CL	No.	No.	CL
"Classic"	23	9 (39%)	27–52%	19	1 (15%)	0.7–17%
Taussig-Bing heart	21	6 (29%)	18–42%	7‡	5 (71%)	45–90%
Others with more-or-less normally positioned great arteries	3	2 (67%)	24–96%	5	1 (20%)	3–53%
Others with D-malposition of aorta	10	4 (40%)	22–61%	6	0 (0%)	0–27%
With L-malposition	3	0 (0%)	0–47%	1	0 (0%)	0–85%
Total	60	21 (35%)	28–42%	38	7 (18%)	12%–27%

* Three patients with situs ambiguus (1 hospital death) are not included.
† Patients with situs inversus totalis (n = 7, 1 hospital death) are included under their situs solitus isomer.
‡ Ages were 1.0, 1.8, 2.5, 4.1, 5.5, 8.2 and 13 months.
CL = 70% confidence limits.

TABLE II Surgical Treatment Other Than Repair for Double-Outlet Right Ventricle,* University of Alabama at Birmingham, January 1967 Through July 1982

Category of DORV	No.	Hospital Deaths	
		No. (%)	CL
"Classic"	18	3 (17%)	7–31%
Taussig-Bing heart	3	1 (33%)	4–76%
Others with more-or-less normally positioned great arteries	3	3 (100%)	39–100%
Others with D-malposition of aorta	8	1 (12%)	2–36%
L-malposition of aorta	4	0 (0%)	0–38%
Superior-inferior ventricle with inlet VSD	3	0 (0%)	0–47%
Total	39	8 (21%)	14%–29%

* Three operations (1 death) in patients with situs ambiguus are not included.

CL = 70% confidence limits; DORV = double-outlet right ventricle; VSD = ventricular septal defect.

Results

Among the 98 patients with DORV subjected to intracardiac repair during the 11-year period, 28 (29%) died in hospital. The overall hospital mortality was lower (18%) in the period since 1977 than in the earlier period (35%, p for difference = 0.08) (Table I). This general trend was also evident in each subset except that with the Taussig-Bing heart. Thirty-nine of the 137 operations (28%) were palliative or were for correction of a major associated cardiac anomaly (Table II).

Operations other than repair: Among the group as a whole, 3 operations were for the repair of associated cardiac malformations. Two neonates with classic DORV and an associated coarctation required initial repair of the coarctation. Both survived. One neonate with the Taussig-Bing heart died after closure of a large patent ductus arteriosus and pulmonary artery banding.

A systemic–pulmonary artery shunt was done as an initial palliative operation before later repair in 19 patients with associated pulmonary stenosis or atresia, with 3 hospital deaths (Table III). In 1971 pulmonary artery banding was done preliminary to repair in 1 patient, who survived.

Sixteen patients were considered to have uncorrectable lesions and underwent definitive palliative operations. Four patients with classic DORV had severe left ventricular or mitral hypoplasia, or both. Two of them had severely restrictive atrial septal defects and were palliated by atrial septectomy. The other 2 had associated pulmonary stenosis; 1 of these died after a Fontan repair and 1 was palliated by a systemic-pulmonary artery shunt (Table III). Two patients with the Taussig-Bing heart and severe pulmonary vascular disease were successfully palliated by a venous switch operation. Seven patients with more-or-less normally related great arteries or with D-position had inlet or trabecular (noncommitted) VSDs associated with other problems, and their defects were considered uncorrectable (Table IV). Two of these 7 patients were explored by open cardiotomy early in our experience, found to be

TABLE III Operations Other Than Repair for "Classic" Double-Outlet Right Ventricle, University of Alabama at Birmingham, January 1967 Through July 1982

Category	1st of Sequential Repairs (n)	Preliminary to Definitive Repair (n)	Definitive Palliation (n)
Uncomplicated		1* (0)	
With PS		11† (2)	
With coarctation	2‡ (0)		
With severe LV and/or mitral hypoplasia			4§ (1)
Total	2 (0) (0%; CL 0–61%)	12 (2) (17%; CL 6–35%)	4 (1) (25%; CL 3–63%)

Numbers in parentheses indicate hospital deaths.

* Pulmonary artery banding, 1971.

† Systemic–pulmonary artery shunting; 1 death in a patient 4 days old, with severe LPA origin stenosis, and small RPA, and 1 death in a 4-day-old baby with pulmonary atresia and absent LPA.

‡ Repair of coarctation.

§ One death after Fontan repair with complex atrial baffle; 2 patients who underwent atrial septectomy and 1 a systemic–pulmonary artery shunt survived.

CL = 70% confidence limits; LPA = left pulmonary artery; LV = left ventricular; PS = pulmonary stenosis; RPA = right pulmonary artery.

TABLE IV Operations Other Than Repair for Double-Outlet Right Ventricle, University of Alabama at Birmingham, January 1967 Through July 1982

Category	Preliminary to Definitive Repair	Definitive Palliation	Total
More-or-less normally related great arteries			
with AV canal type of VSD, severe LV hypoplasia, severe PS		2 (2)*	2 (2)
with AV canal and pulmonary atresia	1 (1)†		
D-malposition			
with trabecular VSD, severe LV hypoplasia, and restrictive ASD		1‖	1
with inlet VSD, PS	3‡	1 (1)§	4 (1)
with inlet and multiple VSDs, PS, RPA arborization anomalies		1‡	1
with inlet VSD, PS, LPA from ductus, severe LV hypoplasia		2‡	2
L-malposition			
with inlet VSD, PS	2‡		2
with outlet VSD and PS	2‡		2
Superior-inferior ventricle and inlet VSD			
with PS		2	2
with PS and multiple VSDs		1*	1
Total	8 (1)	10 (3)	17 (3)

Numbers in parentheses indicate hospital deaths.

* Open pulmonary valvotomy.

† Age 3 days; operation 1971.

‡ Systemic–pulmonary artery shunts.

§ Fontan repair.

‖ Atrial septectomy plus pulmonary artery band.

AV = atrioventricular; LPA = left pulmonary artery; LV = left ventricular; PS = pulmonary stenosis; RPA = right pulmonary artery; VSD = ventricular septal defect.

uncorrectable, and open pulmonary valvotomy was done in the hopes of palliating them, but they died postoperatively. One of the 7 had a restrictive atrial septal defect and was palliated by atrial septectomy. The remaining 4 patients had pulmonary stenosis; 1 died after a Fontan repair and 3 were successfully palliated by systemic–pulmonary artery shunts. Three patients had superior-inferior ventricles and inlet VSDs. They were successfully palliated for their associated pulmonary stenosis, 2 by systemic–pulmonary artery anastomoses and 1 by open pulmonary valvotomy after intracardiac exploration.

Classic DORV: The largest morphologic subset was the group with classic DORV. As noted earlier, 4 of the 59 patients (7%) in this subset were considered uncorrectable, all because of severe left ventricular or mitral hypoplasia (Table III), or both.

Among the 42 patients who underwent repair, 15 had major associated cardiac anomalies (Table V), including 1 with congenital mitral stenosis in whom concomitant mitral valve replacement was done.

Ten hospital deaths (24%) occurred among the 42 patients with classic DORV who underwent repair between 1967 and July 1982 (Table I). Incremental risk factors for hospital death in this group, determined by multivariate logistic analysis, include young age at operation, the type of repair, and the era in which the operation was done (Table VI). The "era effect" is also evident in that from 1978 through July 1982, there was only 1 death (5%, 70% confidence limits [CL] 0.7 to 17%) among the 19 patients who underwent repair (Table VII); the patient who died was one of the 8 in this group <1 year old. The low risk in the current era (1982) is also demonstrated in a nomogram of the multivariate analysis, as is the marked decrease of the incremental risk of young age in the current era (Fig. 1). In the current era, the incremental risk of young age is not evident* unless the patient is as young as 3 months. Specifically, according to the multivariate analysis (Table VI), in the current era when a transanular patch or valved extracardiac conduit is not used, the risk of hospital death after repair in a patient 5 years old is 0.1% (CL 0.01 to 1.1%) and is 3% (CL 1 to 10%) in a patient 3 months old. The increased risk of transanular patching or a valved extracardiac conduit is also not evident in the current era (Table IV), in part because palliative shunting was used in the very young with severe pulmonary stenosis, allowing the repair to be done at an older age.

Repair of Taussig-Bing heart: Two patients with the Taussig-Bing heart were considered uncorrectable because of severe hypertensive pulmonary vascular disease, and were palliated as noted earlier.

The hospital mortality was high in those who underwent repair; 11 of 28 patients (39%; CL 29 to 51%) died in the total experience. The types of repair used varied greatly. When the repair resulted in the left ventricle ejecting into aorta, the hospital mortality was relatively low (1 death in 9 cases). Of the 19 operations in which a venous switch was included, 10 patients died. Multivariate analysis showed "inclusion of a venous switch" to be the only demonstrable incremental risk factor ($p = 0.07$).

Repair of other DORVs with more-or-less normally related great arteries: Two patients in this category and with noncommitted inlet VSDs had complete repair and survived. Six had complete atrioventricular canal defects that extended into the subaortic position, and 3 survived complete repair. Among the 5 patients in this category repaired in the current era (1978 through July 1982), 1 died.

Repair of other DORVs with D-malposition of aorta: Fifteen patients with D-malposition of the aorta but with noncommitted inlet or trabecular VSDs underwent repair, with 3 hospital deaths. One patient with D-malposition and complete atrioventricular canal defect failed to survive repair.

There were no deaths among the 6 patients in this subset operated on in the current era.

Repair of DORV with L-malposition: Of the 4 patients in this subset who underwent repair, none died.

Repair of DORV with superior-inferior ventricle and inlet VSD: Patients in this category have been considered uncorrectable.

TABLE V Surgical Correction of "Classic" Double-Outlet Right Ventricle, University of Alabama at Birmingham, January 1967 Through July 1982 (n = 42)

Major Associated Cardiac Anomalies*	No.	No. of Hospital Deaths
Multiple VSD	6	0
Patent ductus arteriosus	6	1
Pulmonary artery distribution deficiencies or post-shunt stenoses	5	1
Situs inversus totalis	2	0
Unroofed coronary sinus	2	0
Tricuspid incompetence, severe	2	1
Congenital mitral stenosis	1	0
Preoperative LV outflow obstruction	1	1

* Some patients had more than 1 associated anomaly, but in all 15 patients had these anomalies. Three died in hospital (20%).
LV = left ventricular; VSD = ventricular septal defect.

TABLE VI Incremental Risk Factors for Hospital Death After Correction of Classic Double-Outlet Right Ventricle, University of Alabama at Birmingham, January 1967 Through July 1982 (n = 42)*

Variable (Incremental Risk Factor)	Logistic Coefficient ± SD	p Value
Earlier data of operation	−0.043 ± 0.0174	0.01
Young age (logarithm), months	−1.1 ± 0.52	0.04
Use of transanular patch	4.2 ± 1.57	0.008
Use of valved extracardiac conduit	2.7 ± 1.61	0.10

Intercept = 5.4.
* Ten patients who underwent correction of classic double-outlet right ventricle during this period died.

* The incremental risk is considered evident when, as age becomes younger, the lower 70% CL exceeds the upper 70% CL of the plateau risk at older ages.

TABLE VII Surgical Correction of Classic Double-Outlet Right Ventricle, University of Alabama at Birmingham, in the Current Era (1978 Through July 1982) (n = 19)

Pulmonary stenosis	Age	n	Hospital Deaths No.	Hospital Deaths %
NO	<6 mo	5	0	
	6 <12 mo	3	1	
	12 <24 mo	2	0	
	≥24 mo	1	0	
	Total	11	1	9% (CL 1–28%)
YES	<12 mo	0	0	
	12 <24 mo	3	0	
	24 <48 mo	1	0	
	48 <10 yr	2	0	
	≥10 yr	2	0	
	Total	8*	0	0% (CL 0–21%)
Total		19	1	5% (CL 0.7–17%)

* Pulmonary stenosis repair by resection with or without right ventricular outflow tract patch (n = 3), transanular patch (n = 3), transanular patch with orthotopic valve (n = 1), valved extracardiac conduit (n = 1).

CL = 70% confidence limits.

Discussion

DORV is merely 1 type of ventriculoarterial connection, and thus the term embraces a wide spectrum of differing morphologies with differing surgical implications. The morphologic classification used is based on the classic paper of Lev et al in 1973[1] and the recent work of Wilcox et al,[2] and is similar to that we previously described.[6] It takes cognizance of the position of the VSD in the ventricular septum and the position of the great arteries, as well as the relation of the VSD to the great arteries.

Many reports on the results of the surgical treatment of DORV are uninterpretable because the patients are not discussed in clearly defined morphologic subsets. Also, most reports include no mention of cases not repaired, and thus fail to present an accurate picture of the limitations in the surgical possibilities for some types of DORV. This study includes a precise morphologic categorization of all cases, and reviews *all* operations, not just repairs, done for DORV in patients with atrioventricular concordant connection.

The results of repair of correctable classic DORV are now excellent, with an increased risk only in infants <3 months of age (Table VII, Fig. 1). Judson et al[7] found an increased risk in patients <5 years. We previously described the basic technique of the intraventricular tunnel repair.[6,8] The improved results in the recent era are probably related to several factors. Preoperative evaluations have been more complete, allowing more complete repairs. The operations have been more precise and efficient. The routine use of cold cardioplegic myocardial protection has probably contributed to the precision of the operation and the decreased mortality rate. An approach through the right atrium was used for the repair in many patients in this series in the current era, and this may also be helpful in achieving a low hospital mortality rate. A proper geometry for the intraventricular tunnel must not be sacrificed in using this approach. The policy of preliminary shunting in infants with severe pulmonary stenosis similar to that for the tetralogy of Fallot[9] and deferral of repair to about 3 years of age has allowed a low mortality in the current era (Table VII) even when transanular patching or a valved extracardiac conduit is required. Pertinent to this is that the risk of shunting for this malformation is as low as has been reported for tetralogy of Fallot with pulmonary stenosis.[10,11]

A few patients with classic DORV cannot have repair, usually because of severe left ventricular or mitral hypoplasia. Although the mortality rate of the Fontan repair has been high in such patients, properly done it should have an acceptable risk and should provide good definitive palliation if pulmonary vascular resistance is low.

The hospital mortality has been high in patients with the Taussig-Bing heart, and this finding has been reported by others.[12] Luber et al[13] reported only 1 death among 7 patients presumably with the Taussig-Bing heart, but this mortality rate is probably not different (p by Fisher = 0.22) from that reported here. Because of our earlier finding that most late deaths were related to pulmonary vascular disease,[6] operations in the current era have been done in patients during infancy. However, this analysis suggests that the repair should be done by some method other than the one we described earlier,[14] which includes a "venous switch" operation. The explanation is not clear for the high risk of the procedure in these infants or for the fact that it is higher than that of a similar procedure for transposition of the great arteries with VSD. In any event, 1 conclusion is that every effort should be made to do the repair in such a way that the left ventricle ejects into aorta. Only 1 death occurred among the 9 patients in which this was done. Perhaps an arterial switch operation will allow a low hospital mortality.[15] However, the more-or-less side-by-side position of the great arteries found in this subset may at times make such a repair difficult. Perhaps a more determined effort to do an intraven-

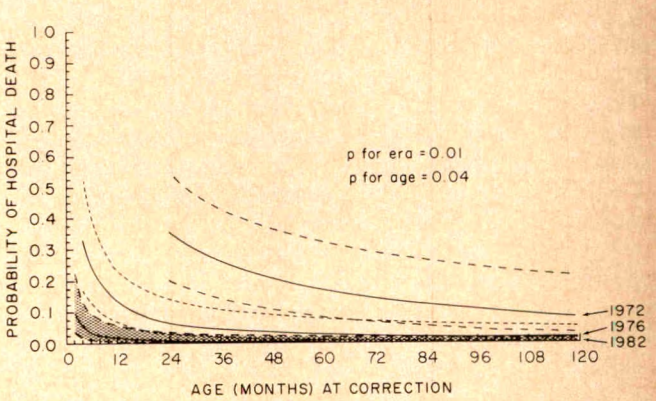

FIGURE 1. Nomogram from multivariate logistic equation (Table VI) for incremental risk factors for hospital death after repair of classic double-outlet right ventricle. The equation was solved using "use of transanular patch—No" and "use of valved extracardiac conduit—No." Three eras of operation (1972, 1976 and 1982) are plotted. The solid lines are the values obtained by solving the equation and the dashed lines enclose the 70% confidence limits. The area enclosed by the confidence limits for 1982 is stippled for ease of reference.

tricular tunnel repair between left ventricle and aorta[16,17] will be more rewarding, using a valved extracardiac conduit between the right ventricle and pulmonary artery when necessary. Because pulmonary stenosis is uncommon in the Taussig-Bing type of DORV, and because pulmonary artery banding is generally unsatisfactory, there is little opportunity to help the situation with a preliminary palliative operation.

Other DORVs with more-or-less normally related great arteries and noncommitted VSDs can usually be repaired unless there is severe left ventricular hypoplasia.[18] Ideally, the repair involves enlarging the VSD, making an intraventricular tunnel between the left ventricle and aorta, and usually placing a valved extracardiac conduit between the right ventricle and the pulmonary artery, because the intraventricular repair in this situation often blocks access to the pulmonary valve.

In the case of other DORVs with D-malposition and a VSD in the inlet or trabecular septum, which are similar to the Taussig-Bing heart except that the VSD is not in the outlet portion of the septum and subpulmonary, operation in the recent era has been performed in somewhat older patients and has carried less risk than in the case of the Taussig-Bing type ($p = 0.02$; Table I). Either type of repair (left ventricle to aorta, or one after which the right ventricle ejects into the aorta and a venous switch has been added) has allowed good results.

In patients with DORV and L-malposition, repair is easily and safely accomplished so that left ventricle ejects into aorta.[19,20] Pulmonary stenosis usually coexists in this entity and the repair is usually done after infancy. A valved extracardiac conduit between the right ventricle and pulmonary artery has been required.

DORV with concordant atrioventricular connection and a superior-inferior position of the ventricles with an inlet VSD is an uncommon malformation. Most examples of the superior-inferior ventricle are in patients with atrioventricular discordant connection, and are not represented in this report. Two of the 3 patients reported here with concordant connection had L-ventricular loop (ventricular inversion) with situs solitus of viscera and atria (criss-cross[4]). In this subset, the interposition of the right ventricle between the left ventricle and either aorta or pulmonary artery, and the position of the inlet VSD, are such as to make an intraventricular tunnel repair nearly impossible. Palliation has been elected, rather than a complex repair including a circuitous valved extracardiac conduit between left ventricle and aorta or pulmonary artery.

Karp, Whelchel, Diethelm and Bargeron (personal communication, 1982) showed that cardiac transplantation can be successful in patients with malpositioned great arteries, and the possibility of this form of definitive treatment at age 10 to 12 years must be kept in mind for children with uncorrectable types of DORV. Therefore, whatever method of palliation is used, the right and left pulmonary arteries should be left in continuity and the great arteries as undeformed as possible.

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Surgical Anatomy of Double-Outlet Right Ventricle—A Reappraisal

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In light of the recent developments in surgical treatment of double-outlet right ventricle, the anatomic observations on this lesion were reevaluated. For this review, double-outlet right ventricle was diagnosed when more than half of both arterial valves were connected to the same ventricle, although appreciating the reasons for using, in a clinical context, a "90% rule" rather than the "50% rule" used in this review. Although this ventriculoarterial connection can exist with any segmental combination, most often it is found in the setting of usually arranged atrial chambers (solitus) and atrioventricular concordance. Categorization of this subset is then done on the basis of the relationships of the arterial trunks. Three main groups stand out: intertwining arterial trunks and "normally related" arterial valves, and parallel trunks, but with the aortic valve to the right side or left side. These groupings give information concerning the site of the ventricular septal defect, which in any group may be perimembranous, muscular or be doubly committed and subarterial. Infundibular morphology is also variable, and the proximity of the arterial valves to the roof of the defect is largely determined by the extent of the ventriculo-infundibular fold.

(Am J Cardiol 1983;52:555–559)

In this issue of the Journal, Piccoli and colleagues[1] from the University of Alabama in Birmingham describe the evolution of their surgical approach to the treatment of double-outlet right ventricle (DORV). They acknowledge the significance of the classic study of Lev and colleagues[2] in influencing their classification, and also refer to our own anatomic study[3] in molding their approach to this malformation. We have been mutually influenced by their surgical experience. Several lengthy discussions with the Birmingham group since the publication of our paper have led to subtle but significant shifts of emphasis in our understanding of the morphology of DORV. In the face of these changes and the accompanying surgical report,[1] it seems appropriate to summarize briefly our current views, concentrating on the benefits they may provide for successful surgical treatment.

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Definition of Double-Outlet Right Ventricle

As Piccoli et al[1] report, we define DORV in terms of a ventriculoarterial connection. In an autopsy study it is much less difficult to determine precisely the connection of overriding arterial valves to their underlying ventricles; therefore, we include within this category all hearts in which more than half of the circumference of both arterial valves are connected to the morphologically right ventricle, and thus include more anomalies than Piccoli et al within this category. However, we appreciate their reasons for using a "90% rule" rather than the "50% rule." As far as both groups of investigators are concerned, the diagnosis of DORV and tetralogy of Fallot are *not* mutually exclusive. Tetralogy of Fallot is diagnosed by its specific outflow tract morphology,[4] which can be found with either a concordant ventriculoarterial connection (aorta connected mostly to the left ventricle) or in the setting of DORV. The finding of a DORV connection does not, therefore, rule out the diagnosis of tetralogy of Fallot. Van Praagh and colleagues[5] recently argued against this approach. However, we see little advantage in a system in which diagnoses must change according to whether or not a small bundle of infundibular musculature separates an arterial from an atrioventricular valve.

Segmental Combinations with Double-Outlet Right Ventricle

Since DORV describes only the ventriculoarterial connection, it can vary considerably in terms of the other segmental connections and associated malformations, as was pointed out by Van Praagh and colleagues.[6] Piccoli et al[1] concentrated on the most frequently encountered combination—DORV in the setting of atrioventricular concordance. Cases with atrioventricular discordance and those with a univentricular atrioventricular connection were excluded from their report. The latter groups comprise a significant number of autopsied hearts studied with DORV, but are rightly excluded from this particular surgical experience. The presence of either atrioventricular discordance, double-inlet ventricle or the absent connection variant of atrioventricular valve atresia completely alters the option for correction.

Piccoli et al[1] also excluded cases with atrial isomerism from their analysis, although tabulating several patients with this atrial arrangement. Recognition of isomeric atrial chambers is an important surgical factor. DORV is by no means an uncommon ventriculoarterial connection in this setting.[7] In the presence of right isomerism ("asplenia"), the almost invariable association with total anomalous pulmonary venous connection predominates. In left isomerism ("polysplenia"), the associated lesions are somewhat less severe but still problematic. Anomalous systemic venous connections are to be expected, particularly azygos continuation of the inferior caval vein, and a common atrioventricular valve is frequently found. The anomalous position of the sinus node also should be noted (Pillai R, Shinebourne EA, Anderson RH, Lincoln C: manuscript submitted for publication). Atrial isomerism should be diagnosed preoperatively by either cross-sectional ultrasonography of the abdominal great vessels[8] or recognition of bronchial morphology by chest radiography.[9] But irrespective of this, the surgeon can routinely exclude atrial isomerism by examining the morphology of the atrial appendages. (Pillai et al: manuscript submitted for publication).

Categorization of Double-Outlet Right Ventricle

The thrust of our earlier paper[3] was that each case of DORV warranted consideration on its own merits. This contention remains valid, but the experience of Piccoli et al shows that the anomalies can be grouped in such a way that the grouping then provides significant surgical information. We have reexamined our morphologic material in this light. As they suggest, grouping according to the relationship of the arterial trunks permits inferences to be made concerning the site of the ventricular septal defect (VSD). The concept of using the interrelationships of the ventricular outflow tracts for classification has long been advocated by de la Cruz and colleagues.[10] The value of this approach for evaluating DORV was highlighted in the studies of Angelini and Leachman[11] and Arteaga et al.[12] Although at first we doubted its significance, further experience has attested to its value. Three subgroupings stand out (Fig. 1). The most frequent arrangement is for the aortic trunk to be situated posteriorly and to the right of the pulmonary trunk and for the great arteries to spiral around 1 another as they leave the base of the heart. This is similar to the arrangement found in the normal heart. In a second large group, the great arteries do not spiral as they ascend, but run in parallel fashion with the aorta to the right. Usually the trunks are also side by side, although there may be some anteroposterior variation, depending on the size of the trunks relative to each other and the position of the heart within the chest. This group is the so-called Taussig-Bing variety. The third group, which is the rarest, has parallel trunks with the aorta anterior and to the left of the pulmonary trunk. We recently observed in life a probably unique patient

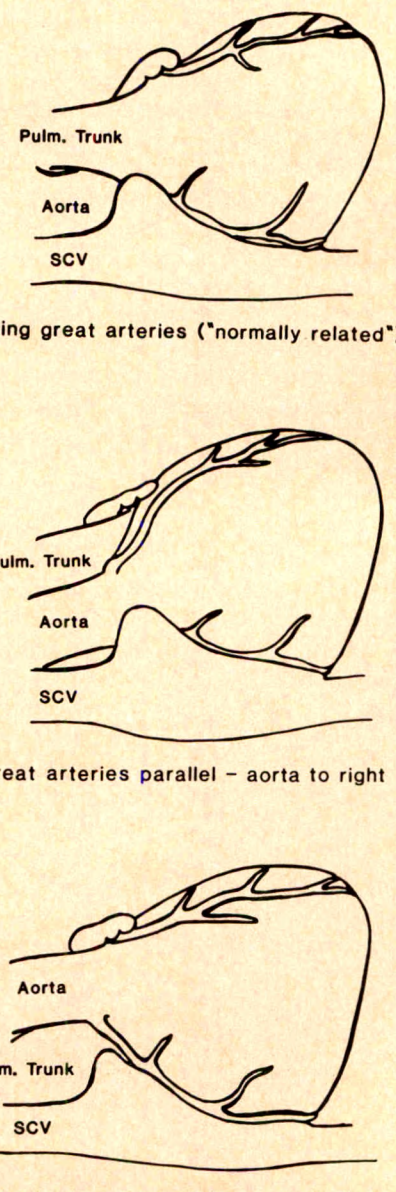

FIGURE 1. The 3 arterial relationships in double-outlet right ventricle as seen by a surgeon. Pulm. = pulmonary; SCV = superior caval vein.

with spiralling great arteries and with the aortic origin posterior and to the left of the pulmonary trunk.

These relationships of the arterial trunks have a definite bearing on the position of the VSD. A VSD is almost invariably present in DORV, and its proximity to the aortic valve is the major determinant of options for surgical treatment. For this reason, previous classifications have rightly focused on the position of the defect relative to the arterial trunks.[2] However, the fact that in different hearts the defect may be subaortic, subpulmonary, doubly committed or noncommitted should not be interpreted in terms of the defect "jumping around" within the septum.[13] Most frequently, the position of the VSD within the septum is standard—cradled between the limbs of the septomarginal trabecula (septal band, Fig. 2). The variability in position relative to the great arteries then depends on the arrangement of the arteries themselves and the orientation and size of the outlet septum. Further differences devolve on the precise morphology of the other muscular or fibrous structures that surround the VSD and form its edges.[14] In this respect, the muscular ventricular septum in hearts with DORV has only inlet and trabecular components. When both great arteries are connected to the right ventricle, the outlet part of the septum ("conal" or "infundibular" septum) is, by definition, an exclusively right ventricular structure.

Morphology of the Ventricular Septal Defect Relative to Arterial Position

Almost without exception, the VSD is cradled between the limbs of the septomarginal trabecula. The rare exceptions are muscular inlet or apical trabecular defects, or when a perimembranous VSD extends posteriorly to occupy mostly the inlet septum. These are the arrangements that produce noncommitted defects, and they can be found in hearts with any arterial relationship. Its relation to the great arteries depends on 2 further factors: the interrelations of the arteries themselves and the morphology and orientation of the outlet septum.

When the great arteries are more or less normally related, then, as shown by Arteaga et al,[12] the line dissecting the 2 arterial valves in their short axis is parallel to the ventricular septum (Fig. 3 left). The outlet septum is then positioned at right angles to the septum. In this arrangement, the outlet septum almost always fuses with the anterior limb of the septomarginal trabecula. The VSD, cradled within the limbs of the trabecula, is thus channeled so as to become subaortic. Rarely the outlet septum itself may be grossly hypoplastic or completely absent. In these circumstances, the defect between the limbs of the trabecula becomes doubly committed. With more or less normally related great arteries, therefore, the defect is usually subaortic, sometimes doubly committed and rarely noncommitted. We have not seen an exclusively subpulmonary defect in this setting.

When the great arteries are more or less parallel with the aorta to the right (the Taussig-Bing group), there is a significant difference of the alignment of the long axis of the arterial valves relative to the septum (Fig. 3 right). The line dissecting their short axis is parallel to the ventriculo-infundibular fold between tricuspid and arterial valves rather than to the septum. Only the left-sided pulmonary trunk is adjacent to the defect in

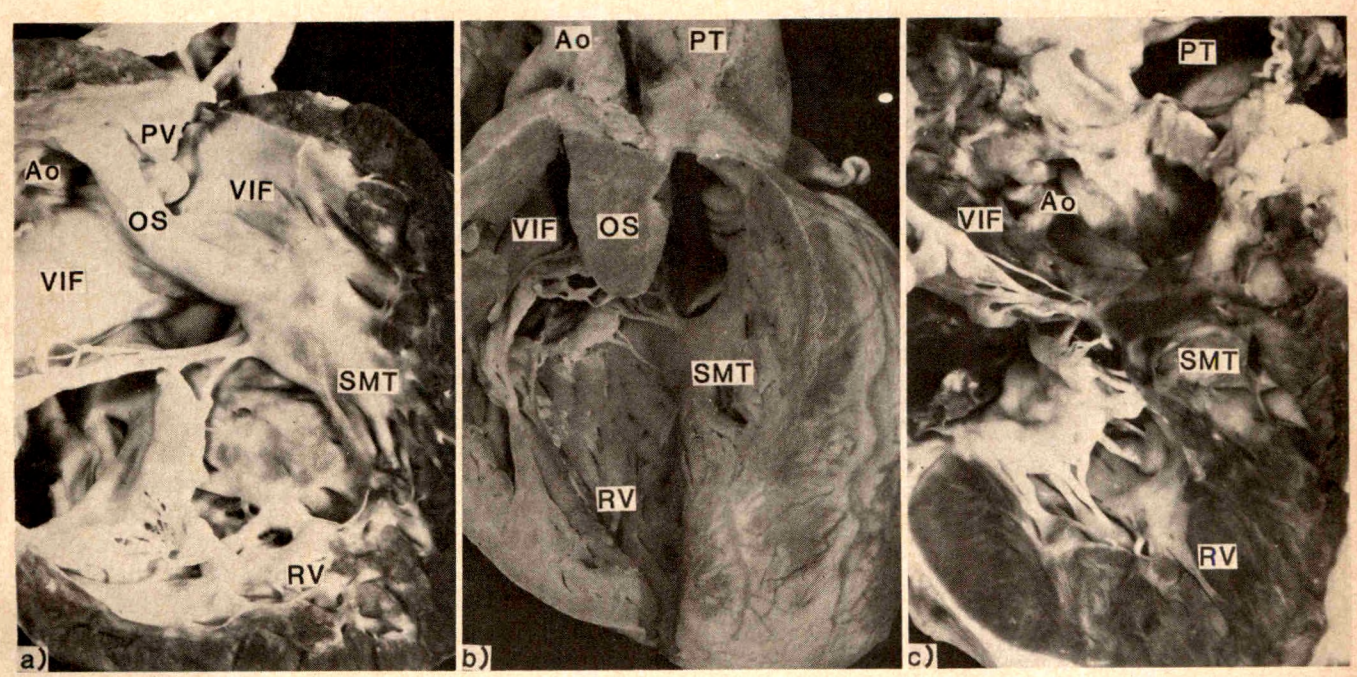

FIGURE 2. The ventricular septal defect in double-outlet right ventricle: **a**, in subaortic, **b**, in subpulmonary, and **c**, in doubly-committed subarterial positions. In each case the defect is between the limbs of the septomarginal trabecula (SMT); it is the attachment of the outlet septum (OS) relative to the ventriculo-infundibular fold (VIF) that varies. The outlet septum is absent in the heart with the doubly-committed defect. RV = right ventricle; Ao = aorta; PT = pulmonary trunk; PV = pulmonary valve.

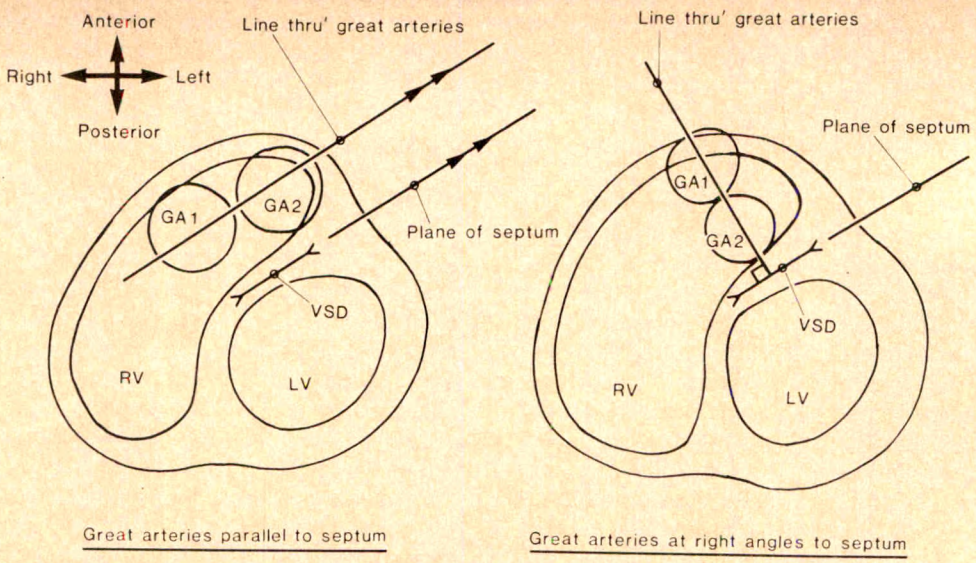

FIGURE 3. The basic difference between the relationship of the arterial trunks and the septum when the great arteries are "normally related" (**left panel**) or when the right-sided artery (almost always the aorta) is anterior (**right panel**). In the latter arrangement, only the posterior and left-sided artery is adjacent to the ventricular septal defect.

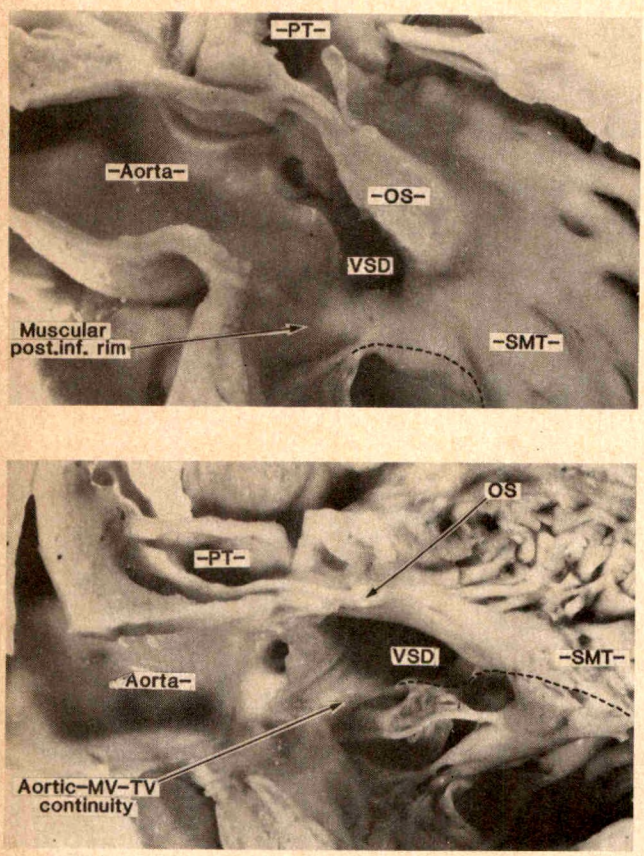

FIGURE 4. Comparison of two subaortic defects. **Upper panel,** the posterior limb of the septomarginal trabecula (SMT) fuses with the ventriculo-infundibular fold to produce a muscular postero-inferior (post. inf.) rim and protects the conduction axis (dotted line). **Lower panel,** these structures are discontinuous so that the defect is perimembranous and the conduction axis is much closer to the rim. OS = outlet septum; PT = pulmonary trunk; VSD = ventricular septal defect; MV = mitral valve; TV = tricuspid valve.

the limbs of the septomarginal trabecula. Thus, fusion of a well-formed outlet septum with the ventriculo-infundibular fold confines the defect to subpulmonary position. Much more rarely, the outlet septum may be absent or hypoplastic and the defect may then be doubly committed.

When the aorta is to the left of the pulmonary trunk, usually the long axis of the 2 arterial valves is parallel to the septum. The most usual arrangement then is for the outlet septum to fuse with the ventriculo-infundibular fold or else be hypoplastic so that the defect is either subaortic or doubly committed. When the defect is doubly committed, there is a tendency for both arterial valves to override, and a spectrum is seen extending toward double-outlet left ventricle. Brandt et al[15] called this "double outlet both ventricles." With a left-sided aorta, the outlet septum may also fuse with the anterior limb of the septomarginal trabecula, so examples can be found with the defect channeled to the posteriorly located and right-sided pulmonary trunk.

Significant Variables in the Boundaries of the Defect

In most examples of DORV, the floor of the VSD is composed of the 2 limbs of the septomarginal trabecula. Its right and left borders may be the outlet septum, the parietal ventricular wall or the ventriculo-infundibular fold, depending on whether the VSD itself is subaortic, subpulmonary or doubly committed (Fig. 2). Further variation depends on the morphology of the ventriculo-infundibular fold itself. When this muscle fold, which by definition interposes between an arterial and an atrioventricular valve,[16] is fused with the posterior limb of the septomarginal trabecula, then the VSD has a muscular postero-inferior rim. This is important to the surgeon because the muscle bundle so formed protects

the conduction tissue axis. In contrast, when the posterior limb does not extend to the fold, then irrespective of the dimensions of the fold itself there will be tricuspid-to-mitral valve fibrous continuity and the defect will be perimembranous (Fig. 4). The conduction tissue axis is then much more vulnerable in the postero-inferior margin of the defect.

The dimensions of the ventriculo-infundibular fold determine whether or not there is a bilateral infundibulum. Although for many years a bilateral infundibulum was considered the hallmark of DORV,[17] Lev et al[2] reported that both great arteries could arise exclusively from the right ventricle when there was arterial-atrioventricular valvar fibrous continuity. Our studies confirmed this finding.[3] This is not to say that the presence of a bilateral infundibulum has no surgical significance. When the fold is well-formed, it constitutes a significant muscle bundle that puts some distance between the VSD and the arterial valves. In contrast, when the fold is attenuated and there is atrioventricular-arterial valve fibrous continuity, the arterial valve is much closer to the defect. In the latter situation it is much easier to close the VSD so as to connect the arterial trunk above it to the morphologically left ventricle.

Conclusions

Cases of DORV can readily be categorized into 3 major subgroups according to the interrelations of the arterial trunks. Because each of these groups is associated with certain specific patterns of VSD, one can predict the relationship of the VSD to the great arteries from the relationship of the great arteries to each other. However, because no rule is perfect, it is much better to obtain each piece of information directly. Recent investigations using cross-sectional echocardiography[18,19] have demonstrated its reliability in identifying the relationship of the defect to the great arteries, and our own work,[20] presently being extended, suggests that it should be possible to recognize the presence of tension apparatus between the defect and the arterial valves, which is also of great surgical significance. Thus, there is little doubt that the categorization of DORV proposed by the Birmingham group gives considerable information for the surgeon and provides a valuable approach for analysis of surgical results. Cross-sectional echocardiography should provide the exact information needed to enable the surgeon to make all preparations and assess the options for operations before entering the operating room.

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Percutaneous Balloon Pulmonary Valvuloplasty

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Percutaneous balloon pulmonary valvuloplasty (BPV) was performed in 18 consecutive patients with valvular pulmonary stenosis (PS) with no associated cardiac defects. The patients were 11 months to 19 years of age. The balloon was positioned across the pulmonary valve and inflated to pressures of 80, 100, and 120 pounds/square inch (psi). Each inflation lasted approximately 10 seconds. Peak systolic pulmonary valve gradient (ΔP) and cardiac output were measured before and 15 minutes after BPV. There was no change in cardiac output, but all patients had an improved ΔP. The prevalvuloplasty ΔP was 81 $\pm$ 31 mm Hg, decreasing to 23 $\pm$ 11 mm Hg after BPV ($p < 0.01$). The right ventricular peak systolic pressure decreased from 106 $\pm$ 31 to 50 $\pm$ 12 mm Hg ($p < 0.01$). No pulmonary regurgitation was noted after BPV. The balloons were 12 or 15 mm in diameter, chosen according to the diameter of the pulmonary valve anulus. Pressures of 100 to 120 psi were required to achieve full inflation of the balloons. BPV also was performed in a patient with tetralogy of Fallot. Subsequent total repair provided an opportunity to observe the mechanism of the dilatation. Evidence of a small tear alongside the anterior valve raphe was noted. BPV induced a significant decrease in ΔP and may offer an alternative method for treating PS. (Am J Cardiol 1983;52:560–562)

Transluminal balloon angioplasty has been increasingly accepted as a nonsurgical technique for dilating stenotic arteries in the peripheral, renal and coronary circulations.[1–4] The recent success of transluminal balloon coronary angioplasty in adults has prompted us and others to apply this principle to children with coarctation of the aorta, pulmonary artery stenosis, and valvular pulmonary stenosis (PS).[5–8] This report describes our experience with the first 18 patients with PS who underwent a nonsurgical percutaneous balloon pulmonary valvuloplasty (BPV).

Methods

Between October 1982 and April 1983, 18 consecutive patients who were thought to have moderate or severe PS diagnosed by auscultation, electrocardiography, pulsed Doppler and 2-dimensional (2-D) echocardiography underwent cardiac catheterization, cineangiography and BPV. The patients were 11 months to 19 years old at the time of BPV. All patients had only PS with no associated cardiac defects. The mean peak systolic pulmonary valve pressure gradient (ΔP) for the entire group was 81 $\pm$ 31 mm Hg (Table I). All patients were premedicated with 0.1 ml/kg body weight of lytic solution (each 1 ml containing 25 mg of meperidine, 6.25 mg of chlorpromazine and 6.25 mg of promethazine) with a maximum of 2 ml given intramuscularly 30 minutes before the procedure.

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Percutaneous right- and left-sided cardiac catheterizations and Fick cardiac output measurements were performed through the right groin. A pullback pressure recording across the pulmonary valve was performed, followed by a right ventricular cineangiogram in the right anterior oblique view. The right-sided cardiac catheter was then replaced by a No. 9Fr balloon catheter (Meditech), which was introduced percutaneously over a flexible tip 0.035-inch guidewire. All balloons used were 40 mm long. The 30-mm length was tried in 2 cases and was replaced by 40-mm balloons because the shorter balloon tended to migrate above or below the valve opening when inflated. The maximal inflatable diameters of the balloons were 12 or 15 mm—at least 1 mm smaller than the diameter of the pulmonary valve anulus as measured on the cineangiogram monitor. To avoid air embolization in the event of balloon rupture, the balloon was inflated and deflated several times outside the patient with a 50/50 mixture of saline solution and contrast medium until all air bubbles were removed. The guidewire was introduced into either the right or the left pulmonary artery and the balloon catheter passed over the guidewire until the middle of the deflated balloon was positioned fluoroscopically across the pulmonary valve. The valve position had been visualized during the right ventricular cineangiogram and marked on the monitor screen. The balloon was then inflated to pressures of 80, 100 and 120 psi. Each inflation lasted approximately 10 seconds. After each inflation, the balloon was deflated and remained so for 2 to 3 minutes before reinflation. The balloon catheter was then replaced by the previous right-sided cardiac catheter. Cardiac output and ΔP were measured again approximately 15 minutes after the BPV, when the heart rate and aortic pressures had returned to prevalvuloplasty levels. A second right ventricular cineangiogram was performed in the right anterior oblique view. The arterial and venous catheters were then

TABLE I Hemodynamic Data Before and After Balloon Pulmonary Valvuloplasty

		Before Valvuloplasty			After Valvuloplasty		
Case	Age	RV (mm Hg)	MPA (mm Hg)	Gradient (mm Hg)	RV (mm Hg)	MPA (mm Hg)	Gradient (mm Hg)
1	2 yr	122/7	16/10	106	32/5	18/6	14
2	13 mo	72/6	18/9	54	45/6	25/9	20
3	11 mo	60/5	25/12	35	45/5	25/12	20
4	3 yr	145/5	25/13	120	55/7	20/10	35
5	8 yr	100/4	25/10	75	45/10	25/12	20
6	3 yr	55/4	22/9	33	32/4	23/10	9
7	9 yr	112/3	35/10	77	55/3	35/15	20
8	2 yr	110/4	23/10	87	38/4	25/10	13
9	9 yr	145/5	30/8	115	65/5	25/6	40
10	19 yr	160/4	20/6	140	57/5	22/8	35
11	4 yr	95/3	30/12	65	45/4	28/10	17
12	12 mo	84/4	25/12	59	40/10	35/15	5
13	13 mo	105/5	30/12	75	40/6	25/13	15
14	13 yr	135/4	25/9	110	70/10	35/15	35
15	5 yr	85/10	32/23	53	55/6	22/12	33
16	4 yr	70/3	25/6	45	40/6	30/15	10
17	2 yr	130/4	22/7	108	70/5	35/16	35
18	14 yr	122/6	30/10	92	65/10	29/12	36
Mean	5 yr	106/5	5/10	81	50/6*	27/11	23*
±SD	±5 yr	±31/2	±5/4	±31	±12/2	±5/3	±11

* $p < 0.01$ compared with prevalvuloplasty values, paired *t* test.
MPA = main pulmonary artery pressure; RV = right ventricular pressure; SD = standard deviation.

removed and a pressure bandage applied overnight. All patients were discharged the next morning and return visits were arranged.

Results

Of the 18 patients, 15 were found to have moderate or severe PS with a resting ΔP of 54 to 140 mm Hg and 3 had mild PS with a ΔP of 33, 35 and 45 mm Hg. No BPV was canceled for technical reasons. All patients had an improved ΔP after the BPV. The prevalvuloplasty ΔP for the entire group was 81 ± 31 mm Hg, and it decreased to 23 ± 11 mm Hg after BPV ($p < 0.01$). The mean cardiac output for the entire group before BPV was 4.56 ± 0.77 liters/min/m^2 and after BPV it was 4.69 ± 0.85 liters/min/m^2.

Subjective comparison of the valve opening and jet stream in the right ventricular cineangiograms performed before and after BPV demonstrated improvement in the valve opening. No patient had evidence of pulmonary valve regurgitation by auscultation and Doppler echocardiography the next day or during the 1- to 6-month follow-up period.

Pressures of 100 to 120 psi were required to achieve full inflation of the balloon. At 80 psi, the balloon assumed an hourglass shape because of the continued resistance of the stenotic valve opening. At 100 to 120 psi, the balloon became fully inflated and cylindrical in shape. When the balloon totally occluded the pulmonary valve, the aortic pressure dropped and was associated with bradycardia, a few premature ventricular beats and restlessness of the sedated patients. When the balloon was deflated, the aortic pressure returned to normal the the aberrant beats disappeared. There was a 5- to 10-minute period of sinus tachycardia after the balloon deflation. Although the balloon ruptured at a pressure of 120 psi in 4 patients, there was no evidence of embolization or ill effects. Three of the balloons that ruptured were 15 mm and 1 was 12 mm in diameter. Inspection of the ruptured balloons after the procedure showed a clean-cut lengthwise tear. On discharge and during the 1- to 6-month follow-up period, the femoral pulses were normal and equal, with no evidence of arterial or venous compromise to the legs.

Discussion

Congenital PS is a common congenital cardiac defect that comprises about 10% of all congenital heart diseases.[9] Surgical valvulotomy is well established and is indicated in moderate and severe PS.[10] Percutaneous transluminal balloon angioplasty has been helpful in certain coronary and peripheral vascular diseases and seems promising in treating PS.

Because of the stiff tapered tip of the catheter, Pepine et al[8] suggested leaving the guidewire protruding through the tip and into the pulmonary trunk to avoid perforation. By choosing catheters with a very short tip distal to the balloon and allowing the distal end of the long balloon to protrude into the left or right main pulmonary artery, the wire can be removed safely. Success in increasing the diameter of the valve opening depended a great deal on a high intraballoon pressure. At 80 psi, the balloon inflated only to an hourglass shape. At 100 to 120 psi, the balloon became cylindrical in shape, indicating that the valve had been opened or stretched to the full diameter of the balloon. This high pressure requirement also was demonstrated in vitro on excised coarctation specimens by Lock et al.[11] To avoid a false change in the ΔP, the pressure measurements after the BPV were performed when the heart rates, aortic pressures and cardiac outputs were approximately equal to the prevalvuloplasty values.

The mechanism of relief of the obstruction in BPV is not well established and may be different from dilatation of the coronary arteries or great vessels. In angioplasty of coarctation of the aorta and pulmonary arterial stenosis, Lock et al[12,13] demonstrated evidence

of tearing of the intimal and medial layers in experimental animals. In pulmonary valvuloplasty, Kan et al[7] assumed that rupture of the valve tissue was a mechanism for the dilatation. In a patient with tetralogy of Fallot not included in this report, we performed the BPV followed by total surgical repair the next day. At surgery, the pulmonary valve was bicuspid, with a tear alongside the anterior valve raphe demonstrating that the mechanism, at least in this case, was by actual tearing of the valve tissue.

BPV as described in this report may offer an alternative method for treating PS. The advantages are that it can be performed in young children when the risk of open-heart surgery is high, can be used as a palliative procedure, does not involve sternotomy, and requires only 2 days of hospitalization. Because it does not involve the use of blood, it may be helpful in treating patients with certain religious convictions.

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Hemodynamic Responses to Ergometer Exercise in Children and Young Adults With Left Ventricular Pressure or Volume Overload

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This study determines (1) the hemodynamic responses to exercise in groups of young patients with either left ventricular (LV) pressure or volume overload, (2) whether these responses differed from healthy subjects when the variables of sex, age, race and body surface area were controlled (analysis of covariance), and (3) whether any of the exercise variables could predict noninvasively the severity of the gradient in aortic valve stenosis (AS). We tested 137 patients, including 70 with AS, 25 with aortic isthmic coarctation, 20 with aortic regurgitation and 22 with mitral regurgitation, and compared them with a control population of 405 healthy children. The children underwent a continuous, graded, maximal test with 3-minute stages. The variables evaluated were peak heart rate, systolic blood pressure, maximal work load (kg-m/min), peak working capacity index (kg-m/min/kg body weight) and ischemia on electrocardiography.

In patients with pressure overload, the maximal exercise values for work load, heart rate and peak working capacity index were significantly different ($p < 0.05$) from control values. The patients with volume overload had higher blood pressure values than either control subjects or patients with pressure overload. Similarly, the values for heart rate in patients with volume overload were lower than values for control subjects and patients with pressure overload. No exercise variable was predictive of severity of AS. These data confirm some previous investigators' findings with respect to LV volume and pressure overload, but do not support the concept that exercise test results are sensitive and specific for the prediction of severity in AS.

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Several studies have demonstrated the usefulness of exercise testing in children and young adults with various forms of congenital and acquired heart disease.[1–12] However, among the studies of controlled, graded exercise testing in children with aortic valve stenosis (AS),[1–9] there is disagreement as to the ability of exercise test data to predict the severity of the obstruction to the left ventricular (LV) outflow tract. Because exercise variables reveal the functional reserve capacities of persons, the exercise test is of critical importance for the evaluation of patients with heart disease. The following variables are frequently measured during exercise testing: blood pressure; electrocardiographic measurements, such as J-point depression and ST-segment slope; heart rate; maximal work load; and peak working capacity index.

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We recently evaluated these variables during upright ergometer exercise in a biracial population of 405 healthy children.[13,14] Significant racial, body surface area–dependent and sexual differences were found for the variables studied. Other investigators have not assessed whether patients with various forms of congenital heart disease differ from normal control subjects in sex, race and body surface area. In this study we determined the hemodynamic responses to exercise in groups of young patients with LV pressure or volume overload and assessed whether these responses differed from normal when using specific control values. In addition, we sought to determine whether any of the exercise variables could be used to predict noninvasively the severity of the disease.

Methods

Patients: We performed exercise tests in 137 patients with LV pressure or volume overload who did not have a shunting lesion. The patients were selected by the child's cardiologist on the basis of the clinical need for the test. LV volume overload was present in 42 patients. Aortic regurgitation was the dominant lesion in 20 and mitral regurgitation in 22. A total

of 95 patients with LV pressure overload were studied, 70 with AS and 25 with coarctation of the aorta. The racial and sexual breakdown showed a black preponderance in acquired lesions and a white predominance in congenital lesions. The patients were 8 to 23 years old (mean ± standard deviation 14 ± 4 years).

The healthy control group of 405 persons was selected from local community centers, day camps or recreational facilities. There were 221 whites and 184 blacks. The data from these studies have been published.[13,14]

The protocol was approved by the Human Assurance Committee and either the parents or patients gave written, informed consent.

Exercise protocol: The technique of exercise testing in our laboratory has been published in detail.[13,14] The children underwent a continuous, graded maximal exercise test to exhaustion on a cycle ergometer, with each stage lasting 3 minutes. Each child was encouraged to exercise to his or her individual maximal effort.

Electrocardiography: Electrocardiographic leads V_5, aVF and V_1 were monitored simultaneously on an oscilloscope. In the healthy control subjects, only lead V_5 was monitored. The electrocardiograms were recorded during the last 10 seconds of each stage. From these tracings, the J-point displacement and the ST-segment slope were measured relative to the PR isoelectric line. This line joins the onset of the p wave to the onset of the QRS and is extended to intersect the ST segment. This method was shown in our laboratory to give a low incidence (2 to 2.5%) of false-positive tests in healthy children.[14] Positive exercise electrocardiograms were defined as those with either J-point displacement >1 mm below the PR isoelectric line, or the tangent to the ST segment, measured 60 to 80 ms after the J point, having a slope ≤0 mV/s.

Heart rate: The heart rate was determined from the electrocardiogram. The heart rate was also displayed on the exercise monitor as a guide to the technician to encourage children who claimed exhaustion at inappropriately low heart rates.

Blood pressure: The systolic blood pressure was determined manually from either arm, unless a coarctation or anomalous subclavian artery decreased the palpable pulse quality. The cuff width was at least two thirds the length of the upper arm. The blood pressure was measured during the last 20 seconds of each stage of exercise and on cessation of exercise (maximal effort).

Work load: The work loads were chosen based on body weight or body surface area, or both. The maximal work load achieved (in kilogram-meters/min) was an average of the work loads completed during the last 2 minutes of exercise. The peak working capacity index was defined as the maximal work load divided by the patient's weight in kilograms. This index is the least biased by variations in age, height or relative body weight.[15]

Severity of disease: Patients with AS were classified into the following 3 groups, based on clinical impression or catheterization data: mild—those with catheterization data showing LV-to-aorta gradients <50 mm Hg; moderate—gradients of 50 to 69 mm Hg; and severe—gradients of 70 mm Hg. If no catheterizations were performed, the clinician estimated severity based on the resting electrocardiogram, physical examination and echocardiographic findings for all the patient groups. No patient had shown severe exercise symptoms, such as syncope or ventricular arrhythmias.

Statistical analysis: The exercise variables from the healthy children were regressed on body surface area. The data were expressed as confidence bands around the regression line, giving predictive values in the 5th, 25th, 75th and 95th percentiles for each body surface area; these plots have been reported.[13,14]

The patient data were compared by an analysis of covariance, with diagnosis, race and sex as the main effects, and body surface area and age as covariates. This testing allowed the comparison between various patient groups and control subjects after the effects of race, sex, body surface area and age had been removed. The significance of these individual differences between groups was assessed with Scheffe's and Tukey's multiple comparison tests;[16] a p value ≤0.05 was considered statistically significant. The exercise variables were analyzed similarly for the patients with AS in relation to the severity of their disease (gradient).

TABLE I Hemodynamic Indexes of Exercise

Diagnosis	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min)	Maximal Work Load (kg-m/min)	Peak Working Capacity Index (kg-m/min/kg)
Pressure overload				
Aortic stenosis	144 ± 26	179 ± 13*	690 ± 276*	13 ± 4*
White males	145 ± 27	179 ± 12	662 ± 276	14 ± 4
White females	137 ± 20	179 ± 15	477 ± 223	11 ± 4
Black males	176 ± 28	178 ± 18	805 ± 327	15 ± 3
Black females	140 ± 14	175 ± 1	500 ± 141	9 ± 2
Coarctation	188 ± 47†	175 ± 19*	678 ± 250	14 ± 4
White males	180 ± 48	176 ± 17	686 ± 256	10 ± 3
White females	159 ± 55	179 ± 5	450 ± 150	10 ± 2
Black males	216 ± 37	170 ± 26	761 ± 236	14 ± 5
Volume overload				
Aortic regurgitation	189 ± 36†	170 ± 16*	599 ± 261	11 ± 3*
White males	207 ± 15	161 ± 8	750 ± 150	13 ± 2
Black males	200 ± 30	172 ± 22	731 ± 294	12 ± 3
Black females	172 ± 41	172 ± 13	431 ± 152	10 ± 3
Mitral regurgitation	154 ± 39	172 ± 19*	607 ± 235	14 ± 4
White males	165 ± 21	183 ± 14	683 ± 363	17 ± 4
White females	119 ± 9	184 ± 26	351 ± 61	13 ± 4
Black males	166 ± 46	161 ± 16	685 ± 208	13 ± 3
Black females	141 ± 12	180 ± 9	675 ± 150	15 ± 3

* Significant ($p < 0.05$) difference from control values.
† Significant difference from values in normal subjects, groups with aortic stenosis and groups with myocardial infarction.
All values are expressed as mean ± standard deviation.

Results

Because of compositional differences among the clinical groups with respect to sex, age, race and body surface area, the mean ± standard deviation of the exercise variables could not be compared legitimately without first controlling specifically for sex, age, race and body surface area. The analysis of covariance approach first assesses and removes the influences of these factors and then determines whether the patients in each clinical group differ from one another and from normal with respect to each exercise variable.

Pressure overload—aortic valve stenosis: The mean level of maximal work load achieved by the patients with AS was significantly higher than that in the control group ($p < 0.05$ by both Scheffe's and Tukey's tests) (Table I). Both the maximal heart rate and peak working capacity were significantly reduced compared with control values. However, there was no significant difference when the maximal systolic blood pressure values were compared with control values. The electrocardiogram interpretation (that is, negative or positive) was not predictive of the severity of the disease (gradient) when analyzed by chi-square testing (Table II). In addition, no other exercise variable was associated with the severity of the gradient.

Coarctation: The maximal systolic blood pressure values were significantly higher than those in the control subjects, and patients with AS and mitral regurgitation. The maximal heart rate values were significantly lower than the control values. The values for both maximal work load and peak working capacity index did not differ from control values.

Pressure overload lesions combined: When the patient groups with pressure overload (AS and coarctation) were combined, their maximal exercise values for work load, heart rate and peak working capacity index were significantly different from control values (Table III).

Volume overload—aortic regurgitation: The mean peak exercise value for systolic blood pressure was significantly higher than that calculated in the control, AS or mitral regurgitation groups (Table I). The values for heart rate and peak working capacity index were significantly lower than those recorded in the control group. The maximal work load results did not differ from control results.

TABLE II Electrocardiographic Interpretation in Patients With Aortic Stenosis: Correlation With Severity

Severity of Disease	Electrocardiographic Intrepretation	
	Normal	Abnormal
Mild	33 (69%)	15 (31%)
Moderate	12 (75%)	4 (25%)
Severe	3 (50%)	3 (50%)

* For definition of severity, see text.

Mitral regurgitation: Although the mean peak values for exercise heart rate were lower than control values, no other variable differed significantly from values in the healthy group (Table I).

Volume overload lesions combined: When the patients with either aortic or mitral regurgitation were combined, they had significantly higher maximal systolic blood pressure values than those recorded in the control and pressure overload groups (Table III and Fig. 1). Similarly, their maximal heart rate was significantly lower than that for both control subjects and patients with pressure overload. In patients with volume overload values for peak working capacity index were significantly lower than values in control subjects, but did not differ from values in patients with pressure overload.

Discussion

Previous investigators have assessed the hemodynamic and electrocardiographic responses to exercise in groups of patients with AS.[1–12] Varying results have been reported, possibly related to whether the control population for comparison was chosen appropriately,

TABLE III Indexes From Pressure and Volume Overload Groups Combined

Diagnosis	Systolic Blood Pressure (mm Hg)	Heart Rate (min^{-1})	Maximal Work Load (kg-m/min)	Peak Working Capacity Index (kg-m/min/kg)
Healthy control subjects	145 ± 26	192 ± 10	558 ± 196	15 ± 4
White males	140 ± 18	193 ± 9	642 ± 248	15 ± 3
White females	142 ± 15	193 ± 9	472 ± 13	13 ± 4
Black males	155 ± 34	191 ± 10	606 ± 182	17 ± 3
Black females	147 ± 34	191 ± 9	507 ± 123	14 ± 3
Pressure overload	154 ± 36	177 ± 15*	627 ± 270*	13 ± 4*
White males	152 ± 35	178 ± 14	668 ± 270	14 ± 3
White females	139 ± 23	179 ± 14	474 ± 213	11 ± 4
Black males	198 ± 38	173 ± 22	779 ± 264	15 ± 4
Black females	141 ± 14	175 ± 1	500 ± 141	9 ± 2
Volume overload	171 ± 41†	171 ± 18†	603 ± 245	13 ± 3*
White males	190 ± 27	172 ± 16	717 ± 251	15 ± 3
White females	119 ± 9	184 ± 26	350 ± 61	13 ± 4
Black males	180 ± 43	166 ± 18	706 ± 243	12 ± 3
Black females	163 ± 37	175 ± 12	506 ± 186	12 ± 4

* Significant ($p < 0.05$) difference from control values.
† Significant difference from values in both normal and pressure overload groups.
All values are expressed as mean ± standard deviation.

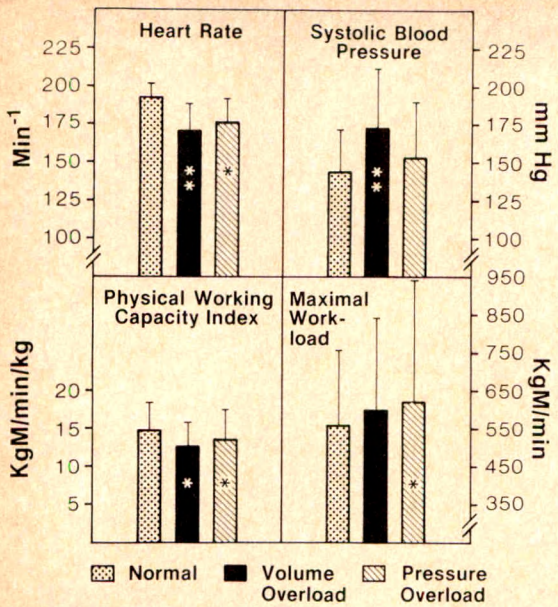

FIGURE 1. Plots of the 4 variables tested, showing the mean ± standard deviation values. * p <0.05 compared with control subjects; **p <0.05 compared with control subjects and pressure overload groups.

the method of analysis, or the variable studied. Recently, we[13,14] described the responses to exercise in over 400 healthy children. These reports defined normal values for maximal work load, peak heart rate, peak systolic blood pressure and peak working capacity index. The results of these studies stressed the necessity of using control values adjusted for sex, race and body surface area.[15] This study describes the comparison between patients with LV pressure or volume overload and specifically adjusted control values.

Blood pressure—aortic valve stenosis: James et al[5] described systolic blood pressure responses in 65 children and young adults with AS to a graded exercise ergometer protocol. Similarities also were noted in the age distribution of the subjects studied by James and those in the present study. The assessment of severity was similar; however, we did not classify the subjects with mild disease into 2 groups with a gradient <50 mm Hg. James noted that peak exercise systolic blood pressure was lower in the groups with gradients >29 mm Hg than in control subjects. The exercise blood pressure measurement did not predict further the severity of the LV to aorta gradient. Whitmer et al[4] reported that compared with preoperative values, peak exercise systolic blood pressure increased significantly postoperatively only when the preoperative gradient was ≥100 mm Hg. In patients with less severe disease, no significant changes occurred.

Previously, Alpert et al[9] showed that if systolic blood pressure increased >35 mm Hg in response to exercise, the probability of a gradient >50 mm Hg was significantly less than with an increase <35 mm Hg. However, many normal persons and patients with gradients <50 mm Hg had exercise blood pressure increases of <35 mm Hg. This limits the value of this observation to patients showing large blood pressure increases.

Blood pressure—coarctation: Several investigators have studied the use of the postexercise systolic blood pressure value in the assessment of the severity of coarctation.[17-21] These authors have stressed the striking increase in systolic blood pressure that occurs both in preoperative patients and in some patients with apparently adequate surgical results. These data suggest that the exercise test, especially with simultaneous arm and leg blood pressure measurement, is an excellent screening tool for patients who need repeat catheterization or operation, or both. The data from our patients with coarctation demonstrated significantly elevated systolic blood pressures compared with data in control subjects and patients with AS or mitral regurgitation. The patients with aortic regurgitation had systolic blood pressure comparable to those in patients with coarctation; the hemodynamic variables in these groups were vastly different. Because no variable could be chosen to accurately reflect clinical severity, we could not classify patients with coarctation into mild, moderate and severe. Similar to our findings, previous investigators[21] have concluded that exercise blood pressure is not a sensitive or specific index of noninvasive evaluation of severity.

Blood pressure—volume overload: The data from this study demonstrated significantly higher blood pressure values in patients with volume overload, but this was an artifact due to the preponderance of patients with AS in the pressure overload group.

Electrocardiography and heart rate: Early studies by Halloran[2] and Chandramouli et al[3] stressed the importance of the exercise electrocardiogram in patients with AS. Both studies reported high sensitivity and specificity for ST-T-wave changes during exercise in patients with gradients >50 mm Hg. Subsequently, Alpert et al[9] could not confirm these findings. The data from this investigation (Table II) confirm Alpert's findings that the exercise electrocardiogram is neither a sensitive nor specific tool in the identification of severity of the gradient in AS. James et al[5] demonstrated an increasing incidence of exercise-induced ST changes in 4 clinical subgroups classified by gradient measurement. For the patients with gradients <50 mm Hg, defined as mild in our series, comparable data from James' patients showed a 37.5% false-positive result. Although it may be argued that any gradient may be associated with an oxygen supply-demand imbalance and that a normal exercise electrocardiogram may be present in a patient with a severe gradient, it is generally accepted that mild gradients should not be associated with significant abnormalities on exercise electrocardiography. The data from our study tend to confirm the necessity of using the PR isoelectric line method of electrocardiographic analysis to insure a low false-positive incidence of ischemia interpretation.

Heart rate: The data from the present study show that both patients with volume overload and those with pressure overload had significantly lower maximal heart rate values than did control subjects (Tables I and III). The subjects with the highest gradients studied by James et al[5] had the lowest heart rate values (p <0.008) compared with values in control subjects. Many of our

subjects had peak exercise heart rate values of about 170 beats/min. This observation was noted by Goldberg et al.[6] We do not believe that our patients performed submaximal tests because their maximal work loads (see later) were in many instances higher than those expected from the control subjects' data. Cumming,[11] using a treadmill protocol, reported peak heart rate values in patients with congenital heart disease comparable with those in control subjects. The difference between modes of exercise (that is, cycle ergometer versus treadmill) may explain some of the apparent differences.

Working capacity: In this study we used 2 indexes of working capacity: maximal work load and peak working capacity index. DuRant et al[15] studied 5 commonly used indexes of physical working capacity and found that the physical working capacity index (kg-m/min/kg) was the least biased by age, height or relative body weight.

James et al[5] expressed their results of working capacity as the total work and the maximal work load achieved. Because the protocol was standardized for all patients, these data represent the same variable—duration of exercise. They found significant decreases in the maximal work load for all of their patient groups compared with control values. The ability of total work or maximal work load to noninvasively predict the gradient in AS was not reported.

The patients in our study with LV volume overload had the lowest values for peak working capacity index. This would suggest that they had less functional reserve capacity than did patients with LV pressure overload. This trend was noted previously[22,23] in patients of similar ages and diagnoses when they were tested doing supine exercise during cardiac catheterization.

Goldberg[10] and Duffie[12] and their associates assessed the usefulness of working capacity as an index of the degree of compromise of the patient with congenital heart disease. Most of the patients with LV pressure or volume overload had normal indexes, and no rigorous statistical analysis was reported to assess the predictive ability of these working capacity values. Cumming[11] expressed his data as the percentile ranges of minutes of exercise on a treadmill protocol compared with the minutes of exercise completed by 2 "normal" groups of children. This approach is essentially the same as that used by James et al[5] and in this study, because duration of exercise translates into a known work load. Cumming could not clearly differentiate patients with severe disease from those with mild or no disease based on this index alone.

Conclusion: The data from this report define the individual hemodynamic and electrocardiographic responses to cycle ergometer exercise and demonstrate the complex interactions of heart rate, blood pressure, working capacity and electrocardiographic interpretation. There were indications that patients with LV volume overload demonstrated more significant impairment in response to graded exercise than did patients with LV pressure overload.

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Aortic Valve Replacement in Childhood: Evaluation of Left Ventricular Function by Electrocardiography, Echocardiography and Graded Exercise Testing

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Preoperative and postoperative left ventricular (LV) performance was evaluated noninvasively in 15 children who survived aortic valve replacement (AVR). The noninvasive evaluation included electrocardiography, M-mode echocardiography, and graded exercise testing. Clinically, there was dramatic improvement postoperatively: All but 2 patients were asymptomatic. No conduction defects or arrhythmias were detected preoperatively; however, in the late postoperative period there was a variety of intraventricular conduction abnormalities, myocardial infarctions, and ventricular or supraventricular arrhythmias. On M-mode echocardiography, children with aortic stenosis continued to have increased LV mass postoperatively. Shortening fraction and left-sided systolic time intervals returned to normal. The children with aortic regurgitation also had persistently abnormal LV mass on echocardiography postoperatively. Exercise data indicated no improvement in working capacity after AVR. Also, 9 children (63%) continued to have ST-segment depression with maximal exercise. These data indicate that AVR does not result in a return to normal of myocardial performance in children with severe aortic valve disease.

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In children, the proper timing of the replacement of a diseased aortic valve with a prosthetic or bioprosthetic device is difficult. Patients with a diseased aortic valve have long-standing left ventricular (LV) volume or pressure overload, and many have had previous unsuccessful surgical attempts at palliation. Operative mortality is high.[1–4] Complications such as perioperative myocardial infarction, low-output syndrome, cerebrovascular accidents, and conduction abnormalities are common.[4] Therefore, several considerations are important when contemplating aortic valve replacement (AVR): What was the preoperative status of LV performance? If preoperative performance was abnormal, was it normalized after surgery? How often and what types of conduction system damage were associated with AVR?

It is well documented that electrocardiography, M-mode echocardiography, and graded exercise testing are safe, reliable noninvasive methods of evaluating LV performance.[5–9] This retrospective study evaluates the changes in cardiac variables before and after AVR in children.

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Methods

Patients: Fifteen consecutive survivors of AVR for aortic stenosis (AS) or aortic regurgitation (AR) between 1964 and 1980 constituted the study group. Thirteen were males and 2 females, aged 11 to 19.5 years (mean 16.3) at the time of surgery. The initial diagnosis was congenital AS in 11 patients, rheumatic AR in 2, and ventricular septal defect (VSD) with AR in 2. Persistent AS (LV-to-aortic gradient >60 mm Hg) was the reason for AVR in 6 children, predominant AR (>3+ on a scale of 0 to 4+ during aortic root angiography) in 5, and combined AS and AR in 4. Both of the children with VSDs had very small left-to-right shunts (pulmonary-to-systemic flow ratio <1.5:1).

AVR was the initial surgical procedure in 11 patients. Four with AS had undergone previous valvotomies. Thirteen mechanical and 7 bioprosthetic valves were implanted. Five children underwent rereplacement of valves. These 5 children with valve failures included the only 2 with fascia lata valves, 1 porcine xenograft, 1 Starr-Edwards, and 1 Björk-Shiley valve. The 2 mechanical valves required replacement because of patient-prothesis mismatch secondary to patient growth. In this group, all studies were performed before attempting AVR and after the most recent surgical procedure. No child has been recatheterized since his most recent AVR.

TABLE I Summary of Electrocardiograms (15 Patients)

Patient	Aortic Valve Lesion	Date of Surgery*	Preop ECG Findings	Postop ECG Findings
1	AR	12/04/79	LVH	PSVT, LVH
2	AS	2/04/65	N	N
3	AS	9/26/78	LVH	MVPC, LBBB
4	AS	7/06/80	LVH	CHB, LVH
5	AS	3/09/71	LVH	VT, MI, LVH
6	AS/AR	1/30/75	LVH	PSVT, LVH
7	AS	3/04/80	LVH	PSVT, LVH
8	AR, VSD	6/27/76	LVH	MVPC, RBBB, LVH
9	AR, VSD	4/10/73	LVH	MVPC, MI, LVH
10	AS	12/09/68	LVH	LBBB
11	AR	9/26/74	LVH	LVH
12	AR	12/20/77	LVH	LBBB
13	AS/AR	2/20/80	LVH	LVH
14	AS/AR	2/20/79	LVH	LVH
15	AS/AR	1/31/80	N	MVPC

* Surgical date is that of most recent procedure.
AR = aortic regurgitation; AS = aortic stenosis; CHB = complete heart block; ECG = electrocardiographic; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; MVPC = multifocal ventricular premature contractions; N = normal; postop = postoperative; preop = preoperative; PSVT = paroxysmal supraventricular tachycardia; RBBB = right bundle branch block; VSD = ventricular septal defect; VT = ventricular tachycardia.

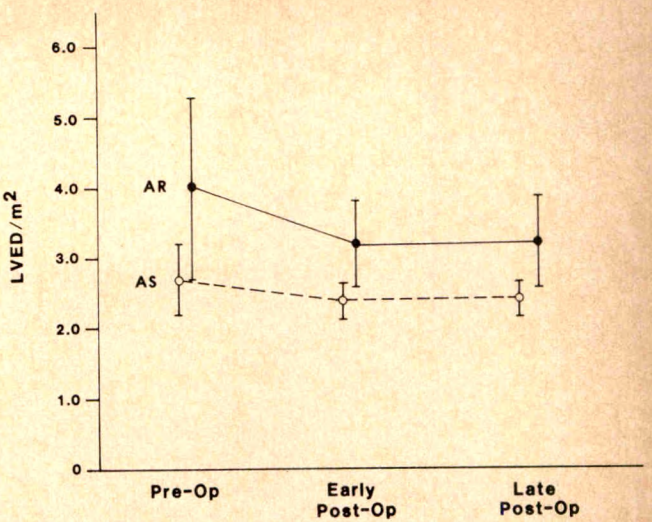

FIGURE 1. Left ventricular end-diastolic dimension index (LVED/m^2), in centimeters, in patients with aortic regurgitation (AR) and aortic stenosis (AS). Measurements were made preoperatively, early postoperatively (<2 months), and late postoperatively (>2 months). The normal index is 2.1 to 3.2 cm/m^2.

Electrocardiograms: All 15 children had standard, 12-lead electrocardiograms performed preoperatively and 2 months to 2 years postoperatively.

Each electrocardiogram was analyzed for signs of LV hypertrophy.[9] ST segments were evaluated for signs of ischemia. Any arrhythmias detected during a standard tracing were recorded on long lead 2 rhythm strips. Each tracing was also scrutinized for signs of conduction delay.

No attempt was made to quantitate changes in the degree of LV hypertrophy pre- and postoperatively because changes in conduction time make prediction inaccurate when using only voltage criteria. Also, T-wave changes (which may indicate LV hypertrophy) are difficult to quantitate.[10]

M-mode echocardiograms: Thirteen children had preoperative echocardiograms. Eleven children had early (<2 months) and late (>2 months) postoperative echocardiograms. The tracings were obtained in a manner previously described.[6] The indexes measured were: (1) LV end-diastolic index (LVEDI) = LV end-diastole/m^2 measured at the Q wave of the simultaneously recorded electrocardiogram. (2) LV preejection period (PEP)/LV ejection time (ET) ratio, measured from the aortic valve echogram.[11] The ratio was chosen rather than the absolute measurements of PEP and ET because this allowed us to make comparisons between groups, independent of differences in heart rate. (3) LV percent shortening (SF%), expressed as the percent change in the LV minor axis dimension from end-diastole to end-systole. (4) Left ventricular wall thickness index, determined by adding LV free wall and septal thicknesses, measured at end-diastole, and divided by the LV end-diastolic minor-axis dimension. (5) Septal motion, expressed as normal or abnormal (defined as deviation from the pattern of anterior motion during diastole and posterior motion during systole [<3 mm excursion]).

Exercise testing: Eleven children underwent preoperative graded exercise testing using the method described by James et al.[12] Ten children had late postoperative tests performed 2 months to 12 years (mean 3.6) after AVR. Working capacity, systolic and diastolic blood pressure responses, and electrocardiographic ST segments were evaluated. The criteria for normal values during exercise have been described.[9] Abnormal ST-segment depression was defined as ST-segment depression in the left precordial leads >1 mm, extending for ≥60 ms after the J point, below the resting P-Q junction level. The variables were measured throughout the period of exercise.[9]

Statistical analysis of all the data included unpaired Student *t* tests of preoperative and postoperative data. Paired *t* testing was not possible because of the small numbers of patients. Analysis of variance was used to determine significant differences between the groups. A p value <0.05 was considered statistically significant.

Results

Clinical data: Four of the patients were asymptomatic preoperatively. Others had complaints of chest pain, dyspnea, excessive fatigue, exercise intolerance, or a combination of these. Postoperatively, 13 patients were asymptomatic. The only 2 symptomatic children had exercise intolerance and 1 had persistent palpitations. None of the patients had murmurs of AR or VSD postoperatively, and only 3 had residual LV outflow tract systolic murmurs. No patient had systemic hypertension pre- or postoperatively at rest.

Electrocardiogram: The pre- and postoperative electrocardiographic data are presented in Table I. Ten children had signs of LV hypertrophy. In the remaining 4 patients, hypertrophy was difficult to assess because of left bundle branch block in 3 and right bundle branch block in one patient. One patient with VSD and AR and 1 with AS (who required enlargement of the small aortic valve ring) had anterolateral myocardial infarctions postoperatively. Three children presented postoperatively with documented paroxysmal supraventricular tachycardia.

The 2 patients who underwent VSD with AR repair and 2 patients in the congenital AS group now have multiform ventricular premature contractions at rest.

Echocardiography: *LVEDI (Fig. 1):* Figure 1 shows the course of the LVEDI (LV end-diastole/m^2) in the patients with predominant AS and predominant AR. The group with mixed AS and AR were classified according to the dominant lesion. The normal index varies

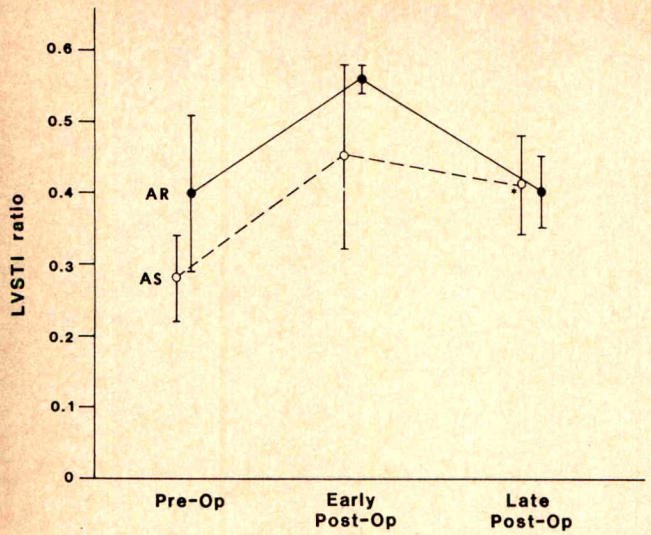

FIGURE 2. Left ventricular systolic time interval ratio (LVSTI) in patients with aortic regurgitation (AR) and aortic stenosis (AS). Measurements were made preoperatively, early postoperatively (<2 months), and late postoperatively (>2 months). *Statistically significant ($p < 0.005$) change from preoperative value. The normal LVSTI ratio is 0.30 to 0.39.

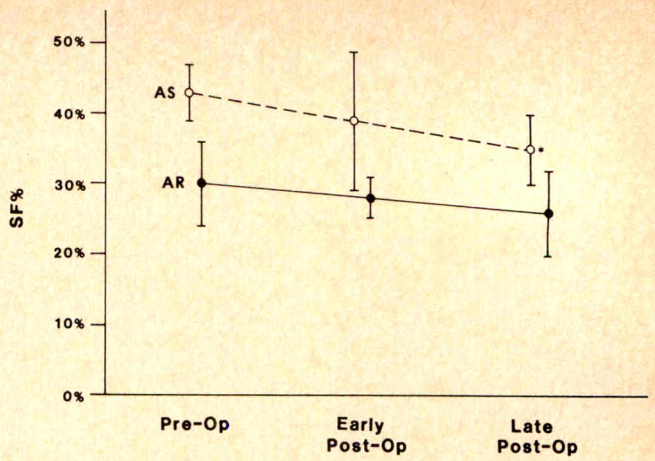

FIGURE 3. Percent left ventricular shortening (SF%) is depicted in both groups of patients (aortic regurgitation [AR] and aortic stenosis [AS]) preoperatively, early postoperatively (<2 months), and late postoperatively (>2 months). *Statistically significant ($p < 0.01$) change from preoperative value. The normal SF% range is 28 to 40%.

from 2.1 to 3.2 cm/m^2.[13] The patients with AS had normal LVEDIs (mean 2.7 ± 0.51) throughout the time course. In the group of patients with AR, the preoperative LVEDI was increased above normal (mean 4.0 ± 1.3). The LVEDI diminished slightly in the immediate postoperative period and remained at the upper limits of normal (mean 3.2 ± 0.67) into the late postoperative period. This change in dimensions was not statistically significant ($p < 0.05$).

LV systolic time interval ratio (Fig. 2): The mean LV systolic time interval (LVSTI) ratio was 0.40 ± 0.10 in the group with AR and 0.28 ± 0.06 in the group with AS during the preoperative evaluation. In the immediate postoperative period, all patients had an increased LVSTI ratio. The 2 patients with left bundle branch block were excluded from the statistics. At the late postoperative study, there was no statistically significant change in the LVSTI ratio in patients with AR. The increase in the ratio in the AS group to normal was significant ($p < 0.005$).

LV percent shortening (Fig. 3): The patients with AS demonstrated hypercontractile left ventricles preoperatively, with a mean SF% of 43 ± 4%. In the late postoperative period, the SF% returned to normal (mean 35 ± 5%). This change was statistically significant ($p < 0.01$). The patient with abnormal septal motion was excluded. The children with AR had a diminished SF% preoperatively and had no significant change in the late postoperative period.

LV wall thickness index (Fig. 4): Children with AS had high LVWTIs preoperatively (mean 0.52 ± 0.10) and did not change significantly after AVR (mean 0.52 ± 0.10). The normal value for the LVWTI is 0.32 ± 0.03 (unpublished data). In the patients with AR, the LVWTI was initially normal. There was an immediate increase in the index postoperatively, followed by a late return to near-normal values (mean 0.33 ± 0.08). The change from preoperative values was not statistically significant.

Septal motion: All patients who had preoperative echocardiograms had normal septal motion. Postoperatively, 5 patients maintained normal motion and 6 children (including all but 1 of the patients with AR) had abnormal septal motion.

Exercise testing (Table II): Preoperatively, none of the 11 patients had working capacities within 20% of expected normal. The systolic blood pressure response to maximum exercise was 12% below normal in the preoperative AS group and 13% above normal in the children with AR. Exercise diastolic blood pressure in the AS patients was generally normal and those with AR had diastolic blood pressures 19% below expected normal.

After AVR, little change was noted in the working capacity for either group. There still is not a single patient who has within 20% of the normal expected working capacity. The systolic blood pressure responses were nearly normal in both groups. The diastolic blood pressure response to maximal exercise was nearly normal in those patients with AS and was 23% above expected normal in the group with AR.

In the preoperative group, 9 of 11 had significant ST-segment depression in the left precordial leads >1 mm at maximal exercise. This included 4 of the patients with predominant AS and all 5 patients with predominant AR. Postoperatively, 4 of 8 children with AS and all 3 patients who had AR preoperatively had ST-segment depression.

Discussion

In adults, the successful correction of LV volume or pressure overload by AVR has resulted in hemodynamic and symptomatic improvement.[5,14–18] Investigators have also been concerned with evaluating the functional status of the LV myocardium after operative repair.[19] Little attention has been directed toward evaluating

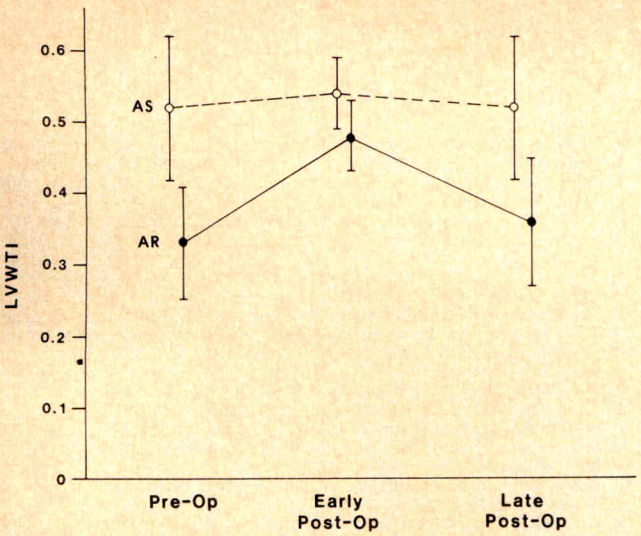

FIGURE 4. Left ventricular wall thickness index (LVWTI) plotted in both groups of patients (aortic regurgitation [AR] and aortic stenosis [AS]). See text for discussion. Preoperative, early postoperative (<2 months), and late postoperative studies (>2 months) were performed. The normal range of LVWTI is 0.29 to 0.35.

these variables in the pediatric and adolescent population.[20]

It is clear that AVR improves most patients symptomatically. Noninvasive evaluation, however, suggests residual LV abnormalities in the majority of children.

The electrocardiographic data preoperatively indicate that LV hypertrophy is the rule in children with AS or AR. Conduction abnormalities and arrhythmias were not detected, although Holter monitoring was not performed. Postoperatively, the majority of patients continue to have electrocardiographic signs of LV hypertrophy. Other abnormalities also occur, including signs of myocardial infarction, left bundle branch block, and right bundle branch block. The production of conduction defects of this type is a well-recognized problem after AVR.[21] In a study by Thompson et al,[22] preoperative conduction defects were noted in 24 to 28% of the adult patients with aortic valve disease. This contrasts sharply with our findings, in which none was demonstrated preoperatively. This might be explained by the shorter duration of volume or pressure overload before surgery, with less development of fibrosis in the area of the conduction system.

Four of the children have developed arrhythmias after surgery and 4 others have developed potentially dangerous ventricular premature contractions.[23] Why supraventricular tachycardia develops is not known. The paroxysmal ventricular tachycardia in the patient requiring aortic ring enlargement is not surprising, particularly after hypothermia and ischemic arrest.[24,25]

The echocardiographic data indicate that preoperatively, children with AS maintain efficient myocardial function by several adaptations. LV muscle mass, reflected by the LVWTI, increases with associated hypercontractility. LV end-diastolic volume is maintained at a normal level. These findings are typical of concentric LV hypertrophy. Studies in adults have suggested

TABLE II Exercise Data*

	Preop		Postop	
	AS	AR	AS	AR
Work capacity	−48%	−51%	−47%	−53%
(Normal/Total)†	(0/6)	(0/5)	(0/8)	(0/3)
SPB	−12%	+13%	−3%	+10%
(Normal/Total)	(1/6)	(4/5)	(2/8)	(2/3)
DBP	0	−19%	+9%	+23%
(Normal/Total)	(4/6)	(2/5)	(4/8)	(0/3)

* All percentages represent mean percent deviation from normal. Negative numbers indicate "below expected normal" and positive numbers indicate "above expected normal."

† First number indicates number of patients with 20% of expected normal value. Second number indicates total number of patients studied.

AR = aortic regurgitation; AS = aortic stenosis; DBP = diastolic blood pressure; SBP = systolic blood pressure.

that in patients with aortic valve disease, the LV volume is generally increased.[26] In younger children, Johnson et al[27] noted that the LV end-diastolic volume was usually decreased. The present study presents data concerning a predominantly adolescent group and perhaps represents an intermediate period in the spectrum of aortic valve disease.

After AVR, LV performance improves, but several abnormalities persist. LV mass remains increased. Although several investigators[15–18] have noted regression of myocardial hypertrophy after AVR, Baxley and Dodge[28] and Gewitz et al[20] noted little regression of LV hypertrophy after relief of obstruction. The reason for the incomplete regression of myocardial hypertrophy is unknown. Carroll et al[29] speculated that in the adult population, causes for a lack of regression could include systemic hypertension or patient-prosthetic mismatch (resulting in obstruction to LV outflow). In this group of children, no child had systemic hypertension at rest. However, the question of size mismatch is important. Since none of the patients have been recatheterized postoperatively, hemodynamic measurements of LV-aortic gradients are unavailable. Certainly, the noninvasive findings in this study group indicate that repeat catheterization is important. Another important question concerning the persistence of LV abnormalities relates to the time span of the study. Myocardial preservation techniques have changed significantly since 1964. With the small number of patients in the group and the long time span, it was difficult to separate the patients for meaningful analysis of different perfusion techniques.

Since 5 patients had valve rereplacements, repeat perfusions may also have contributed to persistent abnormalities of LV performance. However, when these patients were analyzed separately, no significant differences were found in the echographic data after the first and second procedures.

The rise to normal in the LVSTI ratio postoperatively in the patients with AS is most likely related to the physical relief of the obstruction. This reduction in LV afterload also is reflected in the return of the LV %SF to normal.

The children with predominant AR present a different echographic picture. The LVEDI in these chil-

dren were significantly greater than normal and decreased only minimally after surgery. The LVWTI was maintained at near normal preoperatively, indicating the LV muscle mass and dimensions had increased proportionately. Transiently, there was an increase in the ratio postoperatively which most likely indicated a small reduction in LV dimension without a real change in mass. Late postoperatively, the LVWTI returned to normal and, in light of the greater-than-normal LV end-diastole, this would indicate a persistent increase in LV mass.

Implications of these data are that in children with severe AR, LV hypertrophy occurs simultaneously with chamber dilatation, possibly normalizing peak wall stress. These children also have depressed ventricular performance as reflected by diminished working capacity and low echographic shortening fractions. This finding has also been documented in adult and animal studies in long-standing AR.[18,30] Diminished myocardial contractility was probably also reflected by the signs of congestive heart failure in 4 of the 5 patients with predominant AR. After AVR, there was little change in chamber size or thickness. Because most patients with AR have abnormal septal motion postoperatively, overall changes in myocardial contractility are difficult to evaluate.

The exercise data indicate that in both groups of patients there was no improvement in exercise work capacity after AVR. These patients, however, undertook no attempt at conditioning and since exercise capacity was limited for a long period of time before surgery, a great change postoperatively might not be expected.

The lower-than-expected preoperative maximum exercise systolic blood pressure in the group with AS was not surprising. Postoperatively, there was a great deal of scatter in the systolic blood pressure responses in this group; however, the mean was close to normal. The fact that only 2 of 8 patients had a maximal systolic blood pressure within 10% of the normal range suggests persistent LV dysfunction.

In the group with AR, the preoperative maximum exercise blood pressure responses are as would be predicted, with elevated systolic and low diastolic pressures. Postoperatively, only 3 of these patients were exercised, so conclusions are limited.

Preoperative maximum exercise ST segments were depressed >1 mm in 82% of the patients. This was presumably based on a major imbalance in the oxygen supply-demand ratio in the subendocardial region of the myocardium.[9] This response is similar to that illustrated by others[31] in patients with severe AS and AR.

A significant proportion of the children continue to have ST-segment depression with maximum exercise postoperatively. The reason for this finding is not clear. Patients with AS and AR continue to have an increase in LV mass, perpetuating an imbalance in the oxygen supply-demand ratio.

AVR in children, although an uncommon procedure, is an important part of the surgical therapy for severe aortic valve disease. The procedure may be well tolerated in this age group.[32] However, noninvasive evaluation raises questions as to the recoverability performance after AVR.

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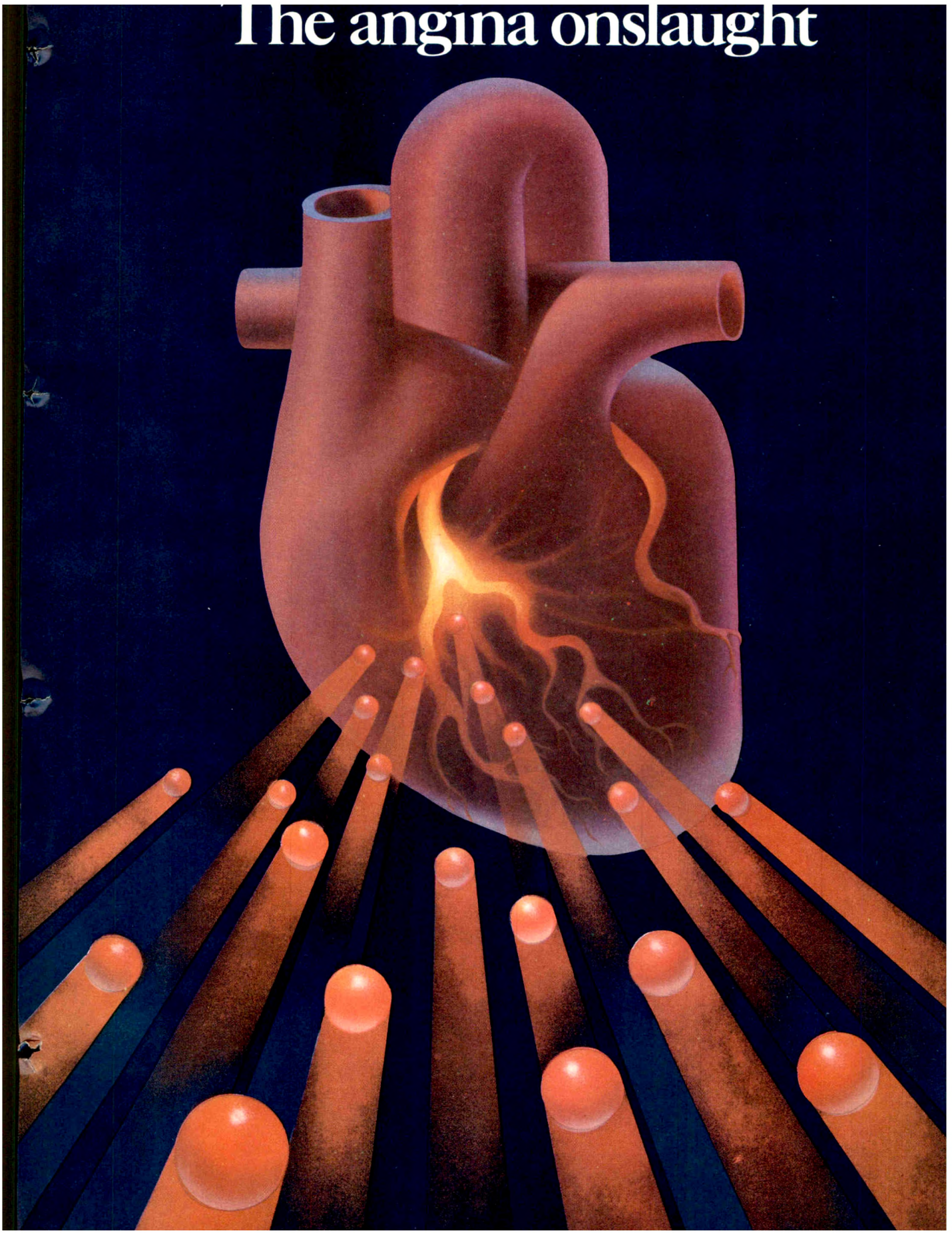
The angina onslaught



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CORGARD®
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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet, in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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Double-Inlet Left Ventricle with Rudimentary Right Ventricle and Ventriculoarterial Concordance

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Seven hearts were studied that had in common the segmental combination of double-inlet left ventricle, rudimentary right ventricle and ventriculoarterial concordance. The prototype of these hearts has been described as the "Holmes heart" or "single ventricle type A1." Five of the hearts had 2 atrioventricular valves; in 1 of these the right valve was minimally straddling. The other 2 had a common valve. In 6 of the hearts the rudimentary right ventricle was obliquely situated on the anterior surface of the dominant left ventricle. The trabecular component was anterior and right-sided with the outlet components and pulmonary trunk in left-sided position. In the final case, both trabecular and outlet components of the rudimentary right ventricle were left-sided. Conduction tissue studies were performed in 2 hearts. In 1, the connecting atrioventricular node and bundle were in anomalous anterolateral position, as expected in double-inlet left ventricle. In the other, a ring-like, posterior, nonbranching bundle connected the regular node in the atrial septum to the branching bundle positioned on the anterior interventricular septum. The anatomic findings are related to the likely modes of presentation and differential diagnosis while the conduction tissue findings are discussed in the light of options for surgical repair. Thus, the term "single ventricle" is best avoided when describing hearts that unequivocally possess 2 ventricular chambers.

(Am J Cardiol 1983;52:573–577)

The anomaly usually called "Holmes heart" has long fascinated those interested in congenital cardiac malformations. First described in 1823 by A. F. Holmes[1] of Montreal, Lower Canada (sic), Rashkind[2] recently suggested that this original heart had atrioventricular valve atresia. However, examination of Holmes' text and illustration, together with study of the heart itself (by kind permission of Dr. A. Dobell), leaves no doubt that the anomaly consisted of double inlet to a left ventricle with a rudimentary right ventricle and ventriculoarterial concordance (aorta from left ventricle and pulmonary trunk from rudimentary right ventricle). Dr. Holmes wrote, with considerable prescience, that his case "might be classified among cases of imperfect double heart, yet it may perhaps be more correctly considered intermediate between them and those of single heart, as from the relations and small capacity of the right ventricle, it can be looked upon only as the commencement of the pulmonary artery."

These comments are still valid in light of the disagreements concerning the propriety of double-inlet ventricle as the criterion of a single ventricle[3,4] and the relation of these hearts to those with tricuspid atresia.[5] In considering these points, the disposition of the atrioventricular conduction tissue axis could also be pertinent. In hearts with double-inlet left ventricle and ventriculoarterial discordance, it is known to be grossly abnormal, the axis originating from an anomalously located anterior atrioventricular node. In the only case of double-inlet ventricle with ventriculoarterial concordance studied histologically of which we are aware,[6] the conduction tissue axis was equally abnormal; it encircled the right atrioventricular orifice but arose from a usually situated posterior atrioventricular node. We have therefore examined the morphologic charac-

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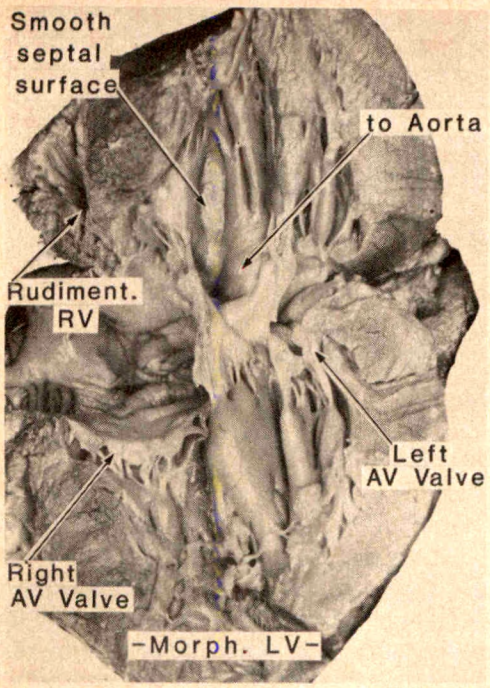

FIGURE 1. The morphologic left ventricle (morph LV) in Case 1. It is connected to both atria through two atrioventricular (AV) valves and gives rise to the aorta. Note the right-sided rudimentary right ventricle (rudiment. RV) and the lack of an inlet septum.

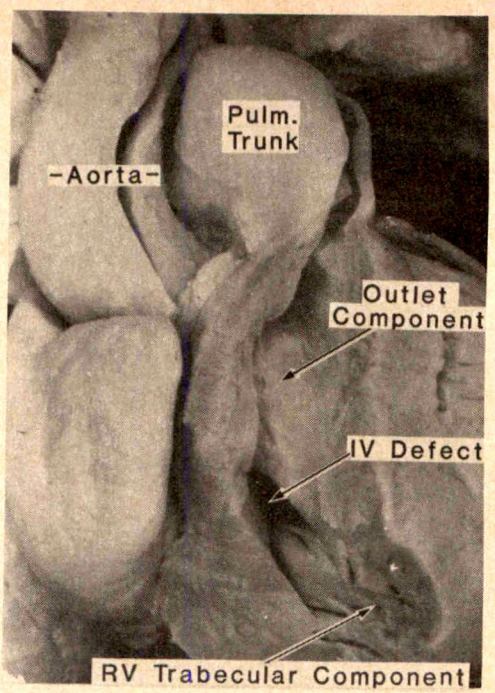

FIGURE 2. The typical morphologic characteristics of the rudimentary right ventricle when the trabecular component is right-sided and the outlet component, supporting a normally related pulmonary (pulm.) trunk, is left-sided. This chamber was from Case 2. Note the stenotic interventricular (IV) communication. RV = right ventricular.

teristics of cases that have double inlet left ventricle and ventriculoarterial concordance.

Methods

In the Heart Museum of the Children's Hospital of Pittsburgh, 5 hearts were found with double-inlet to a left ventricle, rudimentary right ventricle and ventriculoarterial concordance. One similar heart was found in the cardiopathologic collections of the Brompton Hospital, London, and the Royal Liverpool Children's Hospital. Each heart was examined to determine the arrangement of the atrial chambers, the morphologic characteristics of the atrioventricular valves, the size and position of the rudimentary right ventricle and the presence of other associated malformations. Two cases were studied histologically using a technique described elsewhere.[7]

TABLE I Details of Specimens Studied

Heart	Atrial Septum	AV valves	Interventricular Communication	Associated Defects
1	PFO	2 (both MV)	Stenotic	LSVC to CS
2	PFO	1 (Rt-sided Ebstein)	Stenotic	LSVC to CS
3	Intact	2 (Straddling rt)	Adequate	
4	Intact	2 (both MV)	Adequate	LSVC to CS
5	FO defect	1	Adequate	Rt juxta LSVC to CS
6	PFO	2 (both MV)	Stenotic	
7	Intact	2 (both MV)	Adequate	

AV = atrioventricular; FO defect = atrial septal defect at fossa ovalis; LSVC to CS = persistent left superior vena cava to coronary sinus; MV = mitral valve; PFO = patent foramen ovale; Rt = right; Rt juxta = right juxtaposition of atrial appendages.

Results

All 7 hearts had the atrial chambers arranged in usual fashion (solitus). Both the atrial chambers connected in their entirety (or in 1 case mostly) to the dominant ventricular chamber, which had a left ventricular trabecular pattern (Fig. 1). Five hearts had 2 atrioventricular valves, both of mitral pattern with facing squat-like "septal" leaflets that were in extensive fibrous continuity with the aortic valve. The other 2 hearts had common valves, both with 4 leaflets. The right-sided component of 1 of those valves was displaced into the ventricle along the site of the ventricular septum and showed evidence of minimal Ebstein's malformation. In all hearts there was a second anterior rudimentary ventricle that supported the pulmonary valve above a complete muscular infundibulum. It had an apical trabecular component of unequivocally right ventricular type (Fig. 2). In 6 hearts these components were obliquely oriented, with the hypoplastic trabecular component right-sided relative to the aorta, which was connected to the left ventricle, and the pulmonary valve and infundibulum left-sided (Fig. 2). In 1 heart both the subpulmonary infundibulum and the apical trabecular component were left-sided relative to the aorta. In 6 hearts the right ventricle possessed no inlet component and the septum between it and the left ventricle extended to the acute margin of the ventricular mass. In the seventh heart there was minimal overriding and straddling of the right atrioventricular valve so that

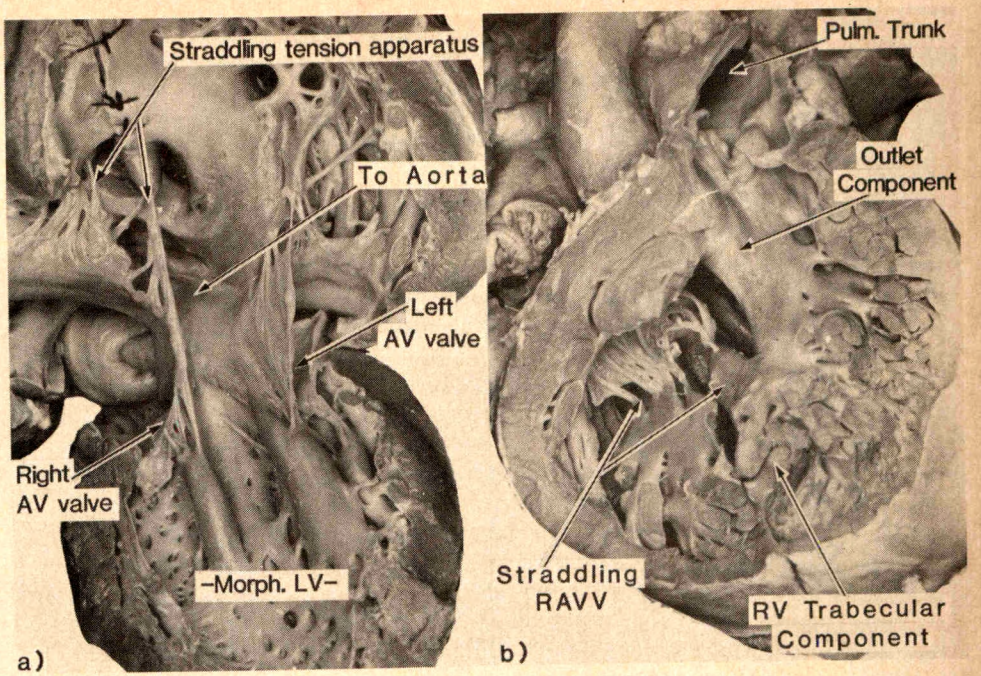

FIGURE 3. The ventricular chambers in Case 3 with minimal straddling of the right atrioventricular (AV) valve. Note the larger size of the interventricular communication and that the atria both connect exclusively to the left ventricle (LV) despite the straddling tension apparatus. **a**, the left ventricle; **b**, the rudimentary right ventricle. RV = right ventricular; Pulm. = pulmonary; RAVV = right atrioventricular valve.

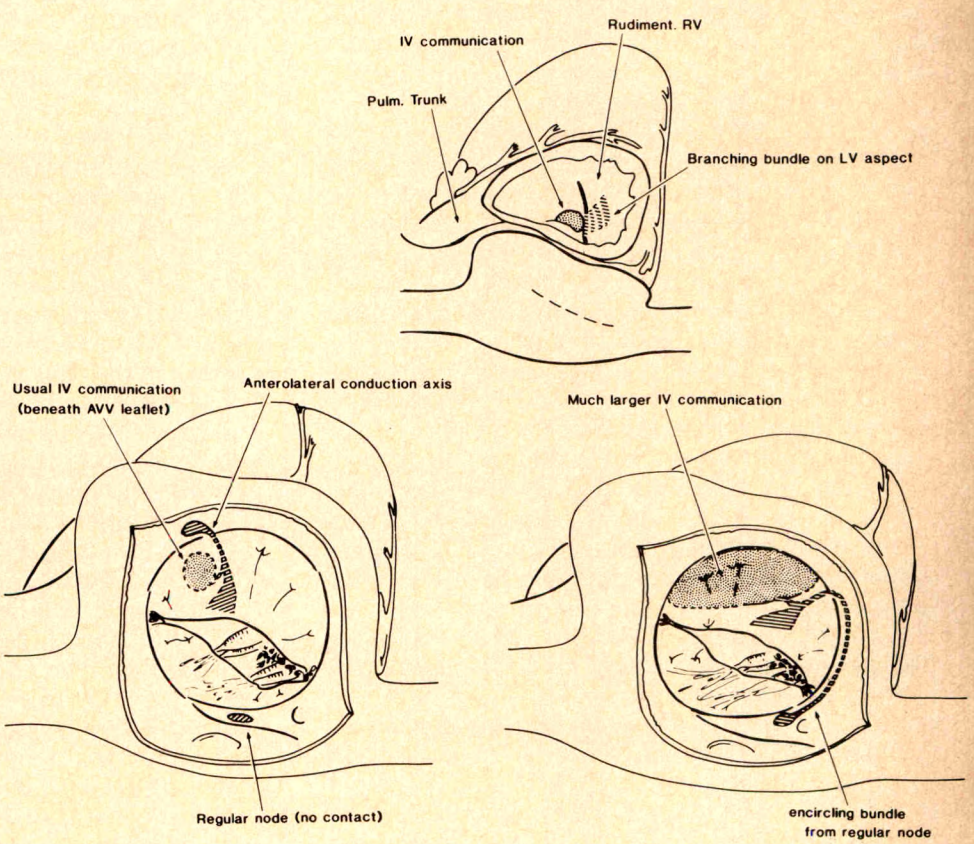

FIGURE 4. The arrangement of the conduction tissues in 2 cases. When viewed from the rudimentary right ventricle (RV), the relationship to the interventricular (IV) communication was the same in both hearts (**upper panel**). The difference would have been evident when the right valve was viewed through the right atrium (incision indicated by **dotted line** in **upper panel**). In the heart from Brompton hospital, there was an anomalous anterolateral node (**lower left**). In the heart from the Liverpool hospital, the septum approached closer to the crux, the IV communication was larger and there was an extensive bundle originating from a regular node (**lower right**). The bundle encircled the posterior aspect of the right atrioventricular orifice. AVV = atrioventricular valve.

some of the tensor appartus attached within the right ventricle (Fig. 3). The septum in this heart inserted to the atrioventricular junction between the acute margin and the crux. Additional malformations are shown in Table I.

The conduction tissue in the heart from Brompton Hospital was disposed in the anticipated fashion for double-inlet left ventricle with ventriculoarterial discordance.[8] There was an anomalous anterolateral atrioventricular node that gave rise to an anterior penetrating bundle (Fig. 4, lower left). A long, nonbranching bundle descended onto the right margin of the interventricular communication and branched beneath the septal crest on its left ventricular aspect. A left bundle branch fanned out in the smooth septal surface of the dominant ventricle and a right bundle branch

penetrated the septum to ramify in the trabecular component of the rudimentary ventricle. A regular node in the atrial septum did not give rise to a penetrating atrioventricular bundle.

The conduction tissue was quite different in the heart from the Liverpool hospital. The septum was orientated so that it fused with the atrioventricular junction much closer to the posterior surface of the heart. A long, nonbranching bundle arose from the regular atrioventricular node in the atrial septum. The bundle initially passed backward toward the crux of the heart before encircling the posterior quadrant of the right atrioventricular orifice (Fig. 4, lower right). It then ran onto the crest of the ventricular septum, where it branched, the fan-like bundle branch spreading out on the smooth left ventricular aspect of the septum and the code-like right bundle branch running through the septum into the rudimentary right ventricular trabecular component (Fig. 4, upper).

Discussion

The hearts described in this report all have both of the atrial chambers connected to the morphologically left ventricle in presence of a rudimentary right ventricle. In all cases the aorta was connected to the left ventricle and the pulmonary trunk to the right ventricle; that is, ventriculoarterial concordance was present. These hearts have been variously described in previous writings. Probably the most popular term is the "Holmes heart," although some might reserve this term for hearts with 2 separate atrioventricular valves as described by Holmes. Some hearts with this segmental combination have also been described as "displaced tricuspid orifice"[9,10] and "single ventricle type A1."[11] The anomaly is of significance with regard to its differential diagnosis, the disposition of the conducting tissues, and particularly to the ongoing discussion concerning the singularity of ventricular chambers.[4] However, although the hearts described had identical segmental combinations, they exhibited significant differences within the segmental group. Five hearts had 2 valves, 1 of these with minimal straddling, and 2 had common atrioventricular valves. Three had stenotic interventricular communications and the others had a large, adequately sized ventricular septal defect. Perhaps more significantly, 6 had the right ventricular trabecular component to the right side of the ventricular mass with the subpulmonary outflow in left-sided position and in 1, both right ventricular trabecular and outlet components were left-sided ("double-inlet left ventricle with isolated ventricular inversion"[12]).

The clinical presentation of cases with this cardiac malformation depends largely on the adequacy of the interventricular communication. If the defect is restrictive, pulmonary stenosis will result, as it does in triscupid atresia with ventriculoarterial concordance. These cases could then masquerade as tetralogy of Fallot. Diagnosis should not be a problem with cross-sectional echocardiography, which is ideal for locating absence of the inlet part of the ventricular septum, the hallmark of the anomaly.[13] When the interventricular communication is large, then the presenting feature will be failure to thrive or frank congestive heart failure. The differential diagnosis will then be a large ventricular septal defect with or without ventriculoarterial discordance ("transposition") or an atrioventricular septal defect ("endocardial cushion defect"). Again, cross-sectional echocardiography can be of great value in making these distinctions, although difficulties may be encountered in those cases with common atrioventricular valve. The key to successful diagnosis is the demonstration of the orientation of the ventricular septum.[14,15] The electrocardiogram will also be of great help in making these diagnoses.

Theoretically, the "Holmes heart" type of double-inlet left ventricle should be amenable to surgical intervention, although experience with this type of heart is limited.[16,17] However, if surgery is attempted either using septation[16,17] or a modified Fontan procedure,[18] knowledge of the precise disposition of the conduction tissue is vital. In our earlier study,[6] which has been confirmed by the present report, we were surprised to find the atrioventricular conduction axis encircling the posterior extent of the right atrioventricular orifice. This finding was unexpected, since from septal disposition we would anticipate an anterior atrioventricular node in these hearts.[6,8] Gross study of the other hearts in the present series also suggested an anterior connection, as in double-inlet left ventricle with ventriculoarterial discordance,[8] and the histologic examination in our first case confirmed this finding. These discrepancies are major problems in predicting the course of the conduction tissue. However, intraoperative mapping should enable the site of the atrioventricular conduction bundle to be determined if necessary. If a modified Fontan procedure is the chosen surgical option, then the atrioventricular node can be avoided by closing the right atrioventricular orifice with a patch secured on the right atrial aspect of the junction at least 1 cm from the valve anulus.[18]

Finally, the morphology of the hearts we are discussing is crucial to the dialectic concerning the appropriate use of the term "single ventricle." Although Ellis[3] and others unequivocally endorsed the initial suggestion of Van Praagh, Ongley and Swan[11] that double-inlet should be the criterion of a single ventricle, more recently Van Praagh, David and Van Praagh[4] altered this stance. Van Praagh and co-workers now consider only double-inlet left ventricle to be a single ventricle.[4] The hearts described in the report unequivocally have double-inlet left ventricle. There can be no doubt that they possess rudimentary right ventricles. Previously, we denied this anterior chamber ventricular status in our zeal to preserve the term "univentricular heart" and to extend its use to hearts with atrioventricular valve atresia. It is now clear to us[19] that the problems our concept produced[4] are best resolved by discontinuing the use of the term "single ventricle" to describe hearts with 2 ventricular chambers. In the present cases, they are well accounted for by the description "double-inlet left ventricle with rudimentary right ventricle and ventriculoarterial concordance." The loss of brevity is more than compensated for by the huge gain in clarity.

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Pulmonary Vascular Development: Normal Values of Peripheral Vascular Structure

SHEILA G. HAWORTH, MD, MRC Path, FRCP, and ALISON A. HISLOP, PhD

Uninjected postmortem normal lung from 49 children aged 1 hour to 14 years was studied using quantitative morphometric techniques to assess arterial size, number and muscularity, particularly in the respiratory region of lung. Arterial size increased most rapidly during the first 2 months of life, but growth rate remained high during the first 4 years. At all ages, the range of values for the mean external diameter of arteries accompanying peripheral airways was considerable, but marked differences from the normal range were usually associated with a marked difference in stature. Arterial number increased rapidly in the first 2 months, but subsequently arteries multiplied at the same rate as alveoli, and the alveolar:arterial ratio was relatively constant. Mean percentage arterial medial thickness fell quickly during the first 10 days and continued to decrease during the first 3 months of life, after which there was little change. The intra-acinar arteries became more muscular during childhood as they increased in size. Vein muscle wall thickness was low throughout childhood. The normal values given in this paper provide a basis for the evaluation of lung biopsies in childhood.

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In the normal child the pulmonary circulation is remodeled in the first weeks after birth as it adapts to extrauterine life. Remodeling continues throughout childhood, although more slowly.[1] The intra-acinar pulmonary arteries increase in size with growth, but also increase in number as new alveoli form. Thus, as the cardiac output increases with age, the pulmonary vascular resistance does not increase. The arteries develop a muscle coat as they increase in diameter. This sequence of events has been demonstrated using injected autopsy lung specimens.[1] Because of the difficulty in obtaining normal material, only 9 injected lung specimens were studied between 3 days and 11 years of age, and only 1 between birth and 4 months. A comparable study of arterial muscularity, size and number has not been made using uninjected tissue. Examination of uninjected lung biopsy specimens in the evaluation of patients with congenital heart disease for cardiac surgery is hampered by lack of information about lung structure in normal children of similar age.[2] Abnormalities of pulmonary arterial pressure and flow and respiratory illnesses, particularly those that cause prolonged hypoxia, can impair the development of the pulmonary circulation.

In the present study uninjected postmortem lung tissue from 49 children was examined using quantitative morphometric techniques to assess arterial size, number and muscularity, the same techniques used to study injected normal tissue. These children died between 1 hour and 14 years of age without cardiopulmonary disease, and 21 were from children <3 months old.

Materials

Lung tissue from 49 children was analyzed. Eight of the children were ≤24 hours, 2 were 6 days, 11 were 1–2 months and 28 were 3 months to 14 years old. All children <3 months had been born at term and no child died with disease of the respiratory or cardiovascular systems. The commonest cause of death was septicemia, in 39% of cases, followed by neurologic (32%), congenital abnormalities of gastrointestinal tract (13%) and malignant diseases (16%). The material was selected from patients who had died at The Hospital for Sick Children from December 1971 through December 1981. No normal lung tissue was found from neonates who died between 24 hours and 6 days of age, since most neonatal deaths were due either to a congenital abnormality of the heart or lungs or to significant pulmonary disease associated with disorders of another system. With few exceptions, lung tissue was analyzed from children who had been growing and developing normally. Eighty-five percent were between the third and 97th centile for height and 71% were at the 50th centile or above. Seven children were below the third centile and 5 died during the first 5 months of life. The male:female ratio was 1.2:1.

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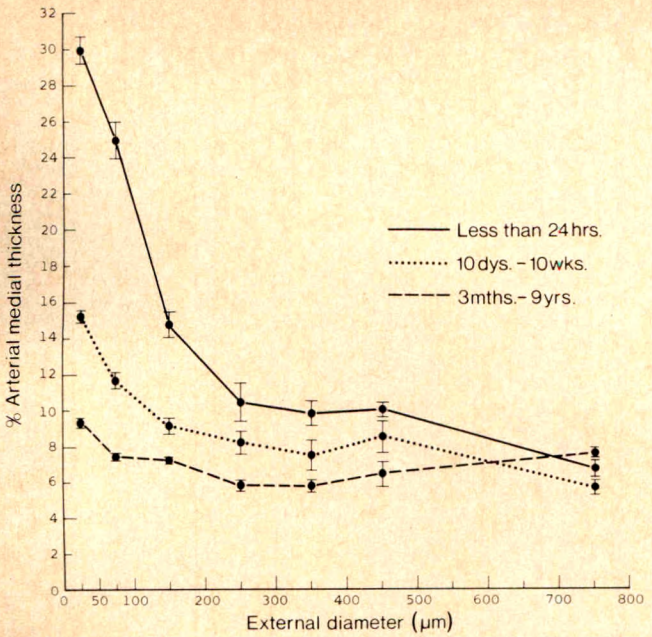

FIGURE 1. Mean percentage arterial medial thickness related to external diameter. Bars indicate the standard error of the mean.

Pathologic techniques: In the tissue studied, neither the arteries nor the airways had been injected under pressure with either fixative or other material. Blocks of tissue were taken at random and 4-μm sections were stained with Miller's stain and counterstained with van Gieson's stain or hematoxylin-eosin. The number of blocks varied according to size of the lung, from transverse sections of both lower lobes in small lungs to 10 blocks taken from each case in older children. All sections were examined qualitatively and quantitatively,[1,3,4] using different microscopes, by both investigators, and there was no significant difference in their results. In each case, arterial medial wall thickness and external diameter of all arteries containing muscle was measured and the percentage medial thickness was calculated. The arteries were grouped according to size, and for each size range the mean percentage of arterial medial thickness was calculated. The mean external diameter and structure (muscular, partially muscular or nonmuscular) of arteries accompanying terminal bronchioli, respiratory bronchioli and alveolar ducts was established.

The size and wall structure of the arteries within the alveolar walls was not studied because in normal persons, these vessels are delicate, easily compressed and may be indistinguishable from small veins. The ratio of alveoli to arteries was determined in 20 to 25 microscopic fields per case. For the veins, mean percentage muscle wall thickness was determined by measuring the thickness of the muscle coat from the internal elastic lamina to the outside of the outermost muscle cell, because there is no external elastic lamina in the normal pulmonary vein. The external diameter and wall thickness was not measured in arteries and veins that had been compressed during fixation or cutting. This reduced the number of larger vessels available for study, particularly those >400 μm in diameter.

The values for percentage arterial medial thickness were pooled into 3 groups: those from children aged ≤24 hours, those from children aged 10 days to 10 weeks and those aged ≥3 months. Differences within each age group and between the age groups were sought using the Student t test. In addition, analysis of variance and Duncan's multiple-range test for variable means was used to discriminate between muscularity in arteries of different sizes and age. To define the relationship between the size of arteries accompanying respiratory and terminal bronchioli and age a polynomial model was fitted. As the age range was from 1 hour to 14 years, log age in weeks was used as the independent variable. Upper and lower 95% confidence limits were calculated by conventional methods.[5]

The lung tissue from each case was not always suitable for the determination of all types of vascular change, as is evident from the Tables.

Results

In all specimens the alveoli had a normal appearance and were inflated, although the degree of inflation varied. None of the cases showed evidence of atelectasis or infection.

Percentage arterial medial thickness: Using the pooled data for percentage arterial medial thickness in each size range, analysis of variance of muscularity with age discriminated between the three groups and showed that percentage arterial medial thickness was significantly lower the older the patient group (Fig. 1, Table I). Duncan's multiple-range test revealed that muscularity was significantly higher the younger the patient group in all arteries <200 μm in diameter at the 5% level. In arteries 200 to 300 μm in diameter, muscularity was significantly greater in children aged 3 months to 9 years than in those ≤24 hours. Using Duncan's multiple-range test, it was not possible to discriminate between percentage arterial medial thickness and age in arteries >300 μm in diameter.

Muscularity of arteries accompanying peripheral airways: The arteries accompanying terminal

TABLE I Arteries: Percentage Medial Wall Thickness Related to External Diameter

		External Diameter (μm)						
Age		0–50	51–100	101–200	201–300	301–400	401–500	501–1000
0–24 hours	n	214	64	35	16	15	4	6
	Mean	29.8	24.9	14.7	10.4	9.8	10.1	6.7
	SD	10.9	6.9	3.7	4.2	2.8	0.8	1.4
10–70 days	n	361	127	71	27	15	9	7
	Mean	15.2	11.6	9.1	8.2	7.5	8.5	5.7
	SD	6.1	5.1	3.1	3.2	2.7	2.4	1.2
0.25–9 years	n	303	189	99	21	11	5	25
	Mean	9.6	7.4	7.2	5.8	5.8	6.4	7.6
	SD	3.4	2.5	1.8	1.5	1.2	1.5	1.7

n = number of arteries; SD = standard deviation.

TABLE II Proportion of Muscular, Partially Muscular and Nonmuscular Arteries Accompanying Peripheral Airways From Birth to 14 Years

		Respiratory Bronchioli			Alveolar Ducts			Age		Respiratory Bronchioli			Alveolar Ducts		
Age	Sex	%M	%P	%N	%M	%P	%N	(yr)	Sex	%M	%P	%N	%M	%P	%N
5 hr	F	54	36	10	17	25	58	6 mos	F	43	57	0	8	84	8
6 hr	M	37	63	0	0	25	75	1	F	100	0	0	3	28	69
11 hr	F	100	0	0	86	14	0	2	F	79	21	0	43	43	14
14 hr	M	35	47	18	0	25	75	2	M	93	7	0	44	44	12
24 hr	M	50	45	5	22	34	44	3	M	75	25	0	46	39	15
6 days	M	45	52	3	20	33	47	3	M	100	0	0	56	40	4
6 days	M	41	59	0	0	57	43	4	M	92	8	0	46	39	15
4 wk	M	67	33	0	45	50	5	4	F	100	0	0	90	10	0
4 wk	M	63	37	0	28	72	0	4	M	96	4	0	33	67	0
4 wk	M	53	47	0	40	40	20	5	M	100	0	0	67	33	0
4 wk	M	76	24	0	28	72	0	5	M	100	0	0	36	64	0
5 wk	M	57	43	0	22	67	11	7	M	100	0	0	83	17	0
5 wk	F	73	27	0	35	65	0	7	F	100	0	0	79	21	0
6 wk	M	94	6	0	48	48	4	9	M	100	0	0	43	57	0
8 wk	M	42	58	0	0	70	30	9	F	77	23	0	60	33	7
9 wk	M	87	13	0	37	42	21	9	M	100	0	0	81	19	0
10 wk	F	88	12	0	29	59	12	10	M	100	0	0	90	10	0
3 mo	F	57	43	0	10	75	15	11	M	100	0	0	94	6	0
4 mo	F	56	44	0	31	50	19	12	F	100	0	0	100	0	0
5 mo	M	0	87	13	0	40	60	14	F	83	17	0	47	41	12

%M = muscular; %N = non-muscular; %P = partially muscular.

TABLE III Mean External Diameter (Micrometers) of Arteries Accompanying Peripheral Airways From Birth to 10 Weeks

	Range (mean)		
Age	Terminal Bronchioli	Respiratory Bronchioli	Alveolar Ducts
5 hr	33–45 (38)	15–38 (26)	10–38 (21)
6 hr	(43)	25–43 (32)	15–28 (21)
11 hr	43–90 (58)	25–55 (36)	18–28 (21)
14 hr	33–45 (40)	20–43 (29)	18–25 (21)
24 hr	28–45 (36)	13–43 (27)	13–25 (18)
6 days*	30–48 (38)	15–38 (25)	13–25 (18)
6 days	40–65 (50)	28–55 (36)	15–25 (20)
4 wk	35–63 (49)	18–38 (26)	15–45 (24)
4 wk	53–98 (67)	28–75 (45)	18–53 (30)
4 wk*	40–75 (55)	25–75 (43)	18–30 (24)
4 wk*	40–50 (44)	23–40 (31)	18–25 (21)
5 wk*	55–110 (80)	20–68 (38)	13–35 (23)
5 wk	53–90 (71)	28–63 (43)	13–35 (23)
6 wk	45–63 (54)	25–63 (36)	13–38 (23)
8 wk*	48–88 (66)	25–65 (39)	15–28 (21)
9 wk	70–113 (93)	25–100 (52)	18–38 (27)
10 wk	50–100 (75)	23–95 (50)	18–43 (29)

* Below third centile for height and weight.
The sex of these patients is listed in Table 2.

bronchioli were entirely surrounded by muscle cells in all but 3 cases, aged 14 hours, 4 weeks and 5 months, when 12 to 25% of the arteries were partially muscular. At respiratory bronchiolar and alveolar duct level the proportion of muscular, partially muscular and non-muscular arteries varied in children of similar age (Table II). However, a pattern of structural change with growth was discernible, the intra-acinar arteries becoming more muscular with age.

TABLE IV Mean External Diameter (Micrometers) of Arteries Accompanying Peripheral Airways From 3 Months to 14 years

		Range (mean)		
Age (years)	Sex	Terminal Bronchioli	Respiratory Bronchioli	Alveolar Ducts
3 mo	F	48–108 (76)	25–105 (47)	13–33 (24)
4 mo	F	43–65 (57)	30–68 (42)	15–33 (25)
5 mo	M	60–91 (78)	26–68 (42)	24–32 (28)
6 mo	F	65–103 (90)	24–68 (43)	26–60 (34)
1	F	60–105 (83)	35–78 (54)	15–44 (32)
2	F	100–140 (117)	23–150 (70)	20–83 (41)
2	M	101–137 (120)	43–101 (64)	22–46 (39)
3	M	109–127 (116)	44–96 (69)	34–62 (44)
3	M	120–155 (133)	42–120 (79)	25–88 (52)
4	M	88–200 (153)	43–123 (85)	28–75 (53)
4	F	91–97 (94)	41–89 (59)	29–55 (39)
4	M	91–140 (125)	56–111 (78)	36–58 (46)
5	M	197–205 (202)	67–108 (85)	33–62 (48)
5	M	142–150 (144)	43–115 (81)	41–65 (48)
7	M	185–195 (190)	50–180 (113)	48–95 (70)
7*	M	110–137 (121)	40–92 (62)	22–50 (37)
7	F	150–245 (180)	53–150 (93)	28–83 (50)
8	F	212–300 (243)	55–157 (105)	30–82 (57)
9	M	152–194 (180)	70–162 (104)	53–87 (65)
9*	F	75–113 (93)	50–118 (77)	35–65 (51)
9†	M	233–300 (266)	98–225 (167)	45–118 (91)
10	M	121–180 (151)	68–139 (98)	48–89 (62)
10	M	193–275 (223)	68–148 (104)	43–100 (62)
11	M	167–320 (264)	75–222 (146)	47–130 (67)
11	F	192–440 (321)	75–207 (140)	60–120 (81)
12	F	(200)	50–225 (138)	43–95 (77)
14	F	248–445 (354)	113–300 (180)	93–175 (130)

* Below third centile for both height and weight.
† Above 97th centile for both height and weight.

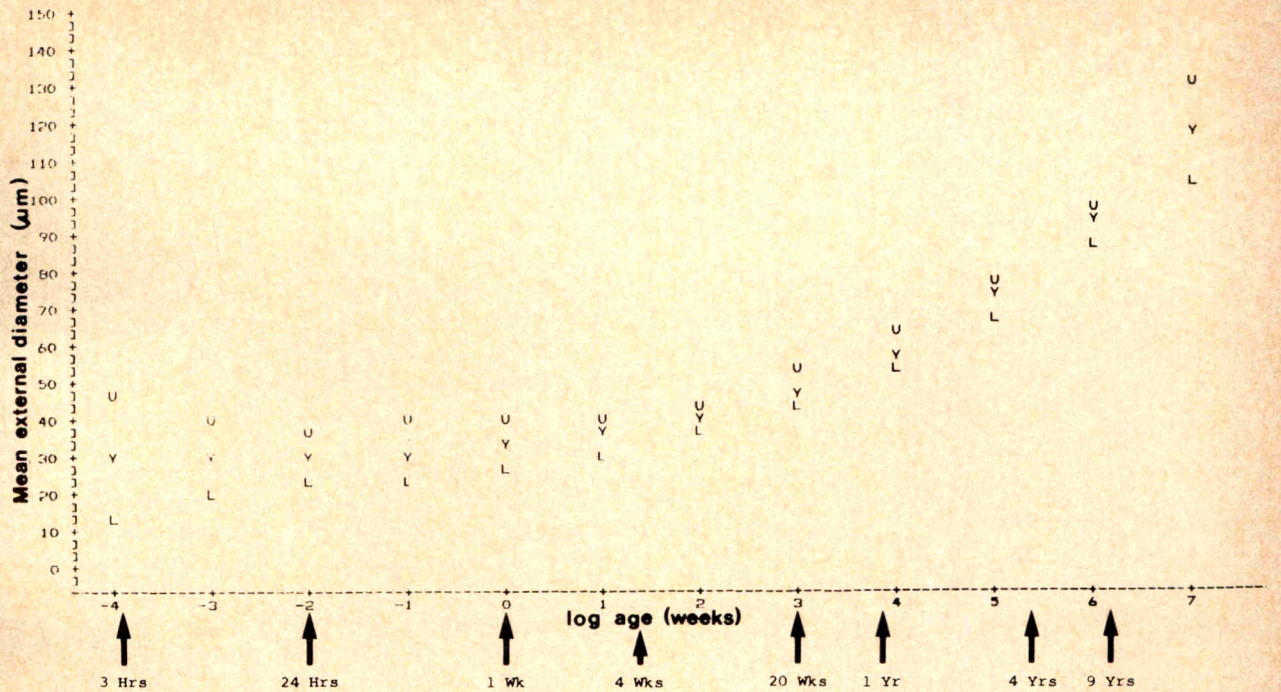

FIGURE 2. A regression line of the cubic polynomial relating mean external diameter of arteries accompanying respiratory bronchioli and age. Y = mean external diameter; UL represents the 95% confidence limits of the relationship.

Intra-acinar arterial size: Arteries accompanying terminal and respiratory bronchioli increased in size most rapidly soon after birth, particularly during the second month of life (Fig. 2, Tables III and IV). The mean external diameter of both types of artery increased steadily with age during the first 4 years, after which the arteries appeared to grow more slowly. A cubic polynomial gave a satisfactory fit to the mean external diameter of both terminal and respiratory bronchiolar arteries and age, giving a residual standard deviation of 9 μm for respiratory bronchiolar size and 27 μm for terminal bronchiolar size. Children in whom the terminal and respiratory bronchiolar arteries were markedly dissimilar in size from those in children of similar age were exceptionally tall or short for their age.

Ratio of alveoli to arteries: The ratio of alveoli to arteries was generally higher in children <8 weeks of age than in older children (Table V).

Percentage vein muscle wall thickness: Normal veins are thin-walled. Percentage vein muscle wall thickness was similar at all ages from birth to 14 years (Fig. 3, Table VI).

Discussion

In autopsy studies examination of both injected and uninjected material gives the most complete assessment of pulmonary vascular structure. However, the material available for study is frequently neither injected nor fixed in inflation. Biopsy tissue is, of course, not injected and inflation is variable.

The present study provides criteria by which to assess the development of the pulmonary circulation in uninjected, but well distended, lung biopsy or autopsy tissue. The period between birth and 2 months is the most difficult to assess the pulmonary vasculature because in normal children, the lung appears to adapt to extrauterine life at varying rates and the range of normal values is greatest at this time.

After birth, pulmonary arterial muscularity decreases at first rapidly and then more slowly, but the findings in the present study suggest that the reduction in muscularity occurs more rapidly than was previously supposed.[1,6–8] During the first 24 hours of life, muscu-

TABLE V Ratio of Alveoli to Arteries With Respect to Age

		Alveolar/Arterial Ratio		
Age	Sex	n	Mean	SD
11 hr	F	24	13.1	6.5
6 days	M	23	13.7	7.5
6 days	M	23	9.2	3.7
5 wk	F	23	14.6	8.6
6 wk	M	23	12.5	6.2
8 wk	M	22	14.3	7.2
9 wk	F	20	9.7	2.8
10 wk	F	22	12.1	7.5
5 mo	M	25	11.7	3.7
6 mo	F	20	12.9	5.2
1 yr	F	21	9.8	3.8
2 yr	F	20	11.2	4.9
2 yr	M	20	9.1	3.4
3 yr	M	20	10.8	4.6
3 yr	M	20	9.1	3.3
4 yr	M	22	9.4	3.3
4 yr	F	21	10.5	4.1
5 yr	M	21	10.9	4.6
5 yr	M	20	10.2	5.3
7 yr	F	21	8.4	3.5
7 yr	M	20	8.9	6.1
9 yr	F	23	8.2	2.9
9 yr	M	20	9.3	3.8
10 yr	M	20	10.4	4.4

n = number of microscopic fields assessed; SD = standard deviation.

TABLE VI Percentage Muscle Wall Thickness Related to External Diameter in Veins From Birth to 9 Years

	External Diameter (μm)						
	0–50	51–100	101–200	201–300	301–400	401–500	501–1000
n	24	106	96	26	15	5	12
Mean	6.3	4.7	4.3	3.9	3.5	2.4	3.0
SD	1.4	1.4	1.4	0.9	0.9	0.5	0.9

n = number of veins; SD = standard deviation.

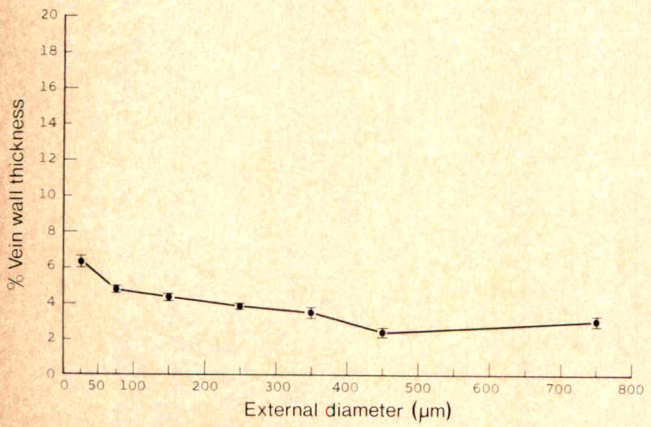

FIGURE 3. Mean percentage vein muscle wall thickness related to external diameter. Bars indicate the standard error of the mean.

larity was high in arteries of all sizes and had decreased significantly by 10 days of age, particularly in arteries <250 μm in diameter. By 3 months, muscularity was at a low mature level in arteries of all sizes. Dammann and Ferencz[6] also used uninjected tissue and found a rapid increase in luminal diameter relative to the width of the media plus intima during the first 2 to 3 months, followed by a more gradual increase. Wagenvoort et al[7] using uninjected tissue, found a rapid reduction in percentage wall thickness during the first 2 weeks of life, and then a more gradual decrease for 18 months. Naeye[8] reported a 30% reduction in medial area during the first week of life. In studies on injected lung tissue, one specimen showed a significant reduction in percentage medial thickness from the fetal level by 3 days of age in arteries <250 μm in diameter and another showed a low adult level of muscularity by 4 months.[1,3] The present study shows that in many—perhaps most—normal children, muscularity probably reaches the low mature level during the first 3 months of life.

Studies on the structure of arteries that accompany peripheral airways showed that as the respiratory bronchiolar arteries increased in size during the first year of life, they acquired a muscle coat. At alevolar duct level the size of the arteries and the proportion of nonmuscular vessels did not change significantly during the first year, suggesting the formation of new precapillary vessels. The 2 processes of formation of new arteries and muscularization of existing vessels appeared to continue until by 4 years of age, nonmuscular alveolar duct arteries were unusual. The majority of these vessels were first partially and then completely muscularized by 7 years of age. The present study suggests that the intra-acinar arteries are more muscular than was suggested in a previous study on injected material.[1] This is probably because of the injection material compressing the vessel walls and making it difficult to discern 1 or 2 smooth muscle cells in a relatively thin-walled normal artery.

The present study provides a basis for the assessment of arterial size in childhood (Fig. 2). In normal children of similar age, the arteries can differ in size, but marked differences in arterial size was associated with differences in height. When assessing a lung biopsy, a reduction in arterial size can only be confirmed when the vessels are shown to be small relative to the height and the age of the child.

The intra-acinar arteries increased in size most rapidly during the second month of life, but the rate of growth remained high during the first 4 years. These findings are similar to those in a previous study on injected tissue[1], but in that study only 6 cases were available for study between 3 days and 4 years of age. Both the injected tissue and the present uninjected tissue studies have shown a greater relative increase in size of the proximal rather than the distal intra-acinar arteries, probably because of the increase in number as well as size of more distal vessels.

The ratio of alveoli to arteries was generally higher during the first 6 months of life than later, when the alveoli and arteries appeared to develop at a similar rate. The alveolar:arterial ratio varied considerably from field to field within any one case. In the normal lung, the number of alveoli per microscopic field of tissue is relatively constant, but the concentration of arteries varies. The number of arteries per microscopic field depends on the part of the acinus being sampled and also on the plane of section. Therefore, as large a number of fields as possible should be sampled in any 1 case. An alveolar:arterial ratio obtained from a small amount of lung biopsy tissue should be interpreted cautiously. In the normal, uninjected lung, it may be difficult to determine the alveolar/arterial ratio because it may be impossible to distinguish small, thin-walled, precapillary arteries from small, thin-walled, postcapillary veins. This explains the relatively small number of results in the present study. However, this is not a problem in the lung biopsies of children with pulmonary hypertension, because the presence of medial hypertrophy makes the distinction between arteries and veins relatively easy.

The thickness of the vein muscle wall was low and did not change with age in this or in previous studies of injected material.[9] In the present study, muscle was found in veins <50 μm in diameter. Wagenvoort[10] found that in adults, muscle first appeared in uninjected veins

40–50 μm in diameter, and Hislop and Reid[9] reported similar findings in the injected lungs of 2 children aged 3 and 10 years.

The findings of the present study will help to assess lung biopsies in children. The greatest variation in arterial structure is seen during the first 3 months of life. Fortunately, relatively few children are biopsied so young. At all ages, the range of normal values is greater in uninjected than in injected material. In the abnormal lung, however, the structural changes are often pronounced and no structural feature is interpreted in isolation, but is related to the other findings in the biopsy. In the lung affected by pulmonary hypertension, for example, pulmonary arterial muscularity is usually considerably greater than normal except when the medial coat has atrophied, as is seen in pulmonary vascular disease grade III or higher;[11] then, other abnormal features are apparent in the biopsy.

The overall growth of the child must be considered when assessing the size of the intra-acinar arteries. This is particularly important in children with congenital heart disease who have severe pulmonary hypoperfusion and are small for their age. In such children, intra-acinar arterial size may be reduced with respect to both age and height.[12]

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Biventricular Function in Sickle-Cell Anemia: Radionuclide Angiographic and Thallium-201 Scintigraphic Evaluation

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Left ventricular (LV) and right ventricular (RV) function were evaluated at rest and during exercise using radionuclide ventriculography in 10 patients, aged 19–53 years, with sickle-cell anemia (SCA). Seven patients were in New York Heart Association functional class I and 3 were in class II. The resting LV ejection fraction (EF) was normal in 9 patients and the resting RVEF was normal in 4. LV dilation and high cardiac output were observed in 6 patients at rest. The LVEF during exercise was normal in all 10 patients, whereas only 2 patients had normal RVEF at rest and during exercise. The LVEF was lower in patients with SCA at rest (54 ± 4% versus 61 ± 6%, p <0.001) and exercise (66 ± 4% versus 74 ± 6%, p <0.001) than in 42 age-matched normal subjects. Rest thallium-201 images from 9 patients showed abnormal RV uptake in 8 and normal LV uptake in 8.

Thus, in adult patients with SCA, LV function was normal during exercise in all patients and at rest in all but 1 patient. The LVEF, however, was lower than that in age-matched normal subjects. RV function was abnormal in most patients at rest and during exercise. RV thallium-201 uptake suggested pressure or volume overload (or both), most likely due to pulmonary vaso-occlusive complications of the disease.

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Most patients with sickle-cell anemia (SCA) show evidence of cardiac dysfunction, manifested principally as fatigue, dyspnea on exertion, cardiac murmur, cardiomegaly and electrocardiographic abnormalities.[1,2] The precise pathophysiologic mechanisms of cardiac dysfunction in these patients have not been well defined. Several mechanisms have been postulated: the effect of anemia[3] per se; thrombotic occlusion of coronary circulation by sickle cells, with resultant myocardial fibrosis;[2,4] cardiomyopathy;[5] iron overload in the myocardium;[6,7] and pulmonary hypertension secondary to repeated pulmonary infarctions.[7–10] Little physiologic information is available regarding ventricular performance during exercise in patients with SCA.[11,12] The purpose of this study was to determine biventricular function at rest and during upright exercise in patients with SCA using radionuclide angiography and thallium-201 scintigraphy.

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Methods

We studied 10 adult patients (6 men and 4 women aged 19 and 53 years; mean 31) with the diagnosis of homozygous SCA previously documented by hemoglobin electrophoresis. These patients had mild symptoms of fatigue, dyspnea on exertion or palpitations. A careful history was taken and physical examination was performed in each patient. None of the patients had a history of angina pectoris, associated cardiac disease or heavy smoking, and there were no physical findings of chronic obstructive lung disease. Although the exact number of transfusions could not be determined, 8 patients (all except patients 6 and 9) had multiple transfusions during childhood. Each patient underwent symptom-limited upright exercise testing; biventricular function was determined by means of first-pass radionuclide ventriculography with a computerized multicrystal camera.[13,14]

Two electrocardiographic leads (CM_5 and aVF) were monitored constantly, and the blood pressure was measured by the cuff method every minute during exercise and the recovery period. Baseline heart rate and blood pressure were recorded, and the upright exercise was begun at a work load of 200 kilopond-meters (kpm)/min, and increased by 100 kpm/min every 2 minutes until the study was completed. The end points of exercise were excessive fatigue, leg weakness or dyspnea.

The methods of exercise testing and measurement of left ventricular (LV) ejection fraction (EF), end-diastolic volume, end-systolic volume, stroke volume, cardiac output and right

TABLE I Clinical Data for 10 Patients With Sickle-Cell Anemia

						Physical Signs						
Patient	Age (yr)/ Sex	Hb (g%)	Hct (%)	Symptoms (NYHA)		LV	RV	Gallop	P_2	Murmur (intensity)	ECG	Med
1	53 M	8.4	26	f	(II)	↑	↑	0	NL	0	LVH	Dig
2	45 M	7.6	23	f/DOE	(II)	↑	↑	0	NL	SEM (II)	ST-T	Dig
3	42 M	7.2	23	DOE	(I)	NL	NL	0	↑	SEM (II)	LVH/RVH	Dig/Fur
4	19 F	7.6	29	DOE	(I)	NL	NL	S_4	NL	SEM (I)	LVH	0
5	23 F	7.4	23	DOE	(I)	↑	NL	S_4	↑	SEM (II)	NL	0
6	21 M	7.5	18	DOE	(I)	NL	NL	0	↑	SEM (II)	LVH	0
7	19 M	7.5	26	DOE	(II)	NL	↑	S_4/S_3	NL	SEM (I)	NL	0
8	28 M	6.5	20	Palp	(I)	NL	↑	S_4	NL	SEM (I)	ST-T	0
9	33 F	10.5	33	Palp	(I)	NL	NL	S_4	NL	0	PRWP	0
10	28 M	8.7	26	f/DOE	(I)	↑	NL	0	↑	SEM (II)	NL	0

↑ = increased; 0 = absent; Dig = digoxin; DOE = dyspnea on exertion; ECG = electrocardiogram; F = female; f = fatigue; Fur = furosemide; Hb = hemoglobin; Hct = Hematocrit; LV = left ventricle; LVH = left ventricular hypertrophy; M = male; Med = medications; NL = normal; NYHA = New York Heart Association functional class; P_2 = pulmonic component of second heart sound; Palp = palpitations; PRWP = poor R-wave progression; RV = right ventricle; RVH = possible right ventricular hypertrophy; SEM = systolic ejection murmur; ST-T = ST-T-wave changes.

ventricular (RV) EF have been described.[13,14] All volumes were indexed by dividing them by the body surface area.

Nine of the 10 patients also underwent rest thallium-201 imaging. The rest images were obtained in 3 projections 20 minutes after intravenous administration of 2 mCi of thallium-201. This technique has been described.[15] The thallium-201 images were assessed for the presence or absence of perfusion defects in the LV images as well as for uptake in the region of the right ventricle. The RV thallium uptake was compared with the LV uptake and graded on a scale of 0 to 3: 0 = no uptake, 1 = mild uptake, 2 = moderate uptake and 3 = severe uptake equal to that of LV uptake.

Statistical analysis: Statistical analysis was performed by analysis of variance or the Yates-corrected chi-square test for differences between groups. Differences between rest and exercise measurements were analyzed by means of a 2-tailed paired *t* test. Values were expressed as the mean ± standard deviation (SD) when appropriate. A probability (p) value <0.05 was considered significant.

Results

The pertinent clinical data for the study patients are listed in Table I.

The exercise was terminated because of fatigue in 9 patients and dyspnea in 1 patient. The exercise capacity was abnormal (<7 minutes) in 7 patients. (In our laboratory, patients with no underlying cardiovascular disease have an exercise capacity of ≥7 minutes.[16]) None had chest pain during exercise.

Left ventricular function: The resting LV function was normal (EF ≥ 50%) in 9 patients and mildly decreased in 1 patient (no. 6). The resting end-diastolic volume was increased (>100 ml/m^2) in 6 patients and was normal in 4. The exercise LVEF was normal (≥55%) in all 10 patients. The response to exercise was normal (≥5% increase) in 8 patients. One of the 2 patients with <5% increase (no. 7) had a resting heart rate of 120 beats/min; thus, the resting EF in this patient was already increased. The other patient (no. 10) had a 4% increase in EF during exercise (Table II). The LVEF was lower in patients with SCA at rest (54 ± 4 versus 61 ± 6%, $p<0.001$) and during exercise (66 ± 4 versus 74 ± 6%, $p<0.001$) than in 42 age-matched normal subjects. These subjects were 7 to 35 years old (mean 25 ± 6) and had a low probability of coronary heart disease and no other recognizable heart diseases.

There was no significant change in LV end-diastolic volume with exercise (131 ± 41 ml/m^2 at rest versus 114 ± 27 ml/m^2 during exercise; difference not significant [NS]). Individual responses are listed in Table II. The cardiac index increased in all 10 patients during exercise. Patients 3 and 9 had at least a 3-fold increase in cardiac index, Patients 1, 4, 6, 8 and 10 at least a 2-fold increase and Patients 2, 5 and 7 less than a 2-fold increase. The increase in cardiac index with exercise was mediated primarily by an increase in the heart rate, because the stroke volume did not change significantly with exercise (69 ± 20 ml/m^2 at rest versus 75 ± 14 ml/m^2 during exercise; NS).

Right ventricular function: The RVEF at rest was normal (≥40%) in only 4 patients. An increase in RVEF during exercise (≥5%) was seen in patients with normal or abnormal resting REVF. However, only 2 patients had normal RVEF at rest and during exercise. In our laboratory a normal RVEF obtained in 12 subjects is 46 ± 7% and 57 ± 9% during exercise ($p<0.001$). Of the 8 patients with a loud pulmonary component of second heart sounds or RV enlargement by physical examination (Table I), 7 had abnormal RV function at rest or during exercise (or both).

Rest thallium-201 imaging: The rest thallium-201 images showed a normal LV perfusion pattern in 8 of 9 patients. Patient 1 had a mild decrease in perfusion of the inferior wall. This patient was the oldest in the group, had a normal LVEF and wall motion at rest and during exercise, and had a normal LV size. Abnormal RV uptake (grades 1 or 2) was present in 8 of 9 patients (Fig. 1). Abnormal RV uptake was not seen in any of 60 patients who had normal rest thallium-201 images in our laboratory. The RVEF was abnormal at rest or during exercise in 7 of 8 patients with RV visualization on thallium scintigraphy. The RV uptake was mild (+1) in 7 patients and moderate (+2) in 1 patient (no. 1). Patient 9, who had no RV uptake, had not had prior transfusions and had normal LV size and a normal LVEF. This patient had a mildly decreased RVEF at rest, but a normal response to exercise.

TABLE II Resting and Exercise Hemodynamics in 10 Patients With Sickle-Cell Anemia

	Blood Pressure (mm Hg)		Heart Rate (beats/min)		LVEF (%)		RVEF (%)		EDVI (ml/m²)		ESVI (ml/m²)		SVI (ml/m²)		CI (l/min/m²)			
Patient	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	Ex (min)	Wrk (kpm/min)
1	140/100	190/100	83	146	54	74	30	49	78	69	36	18	42	51	3.5	7.1	3.3	200
2	140/80	160/80	49	104	58	66	16	20	167	132	70	45	97	87	4.7	9.0	2.2	200
3	120/80	200/70	70	159	54	67	50	25	158	101	73	33	85	68	5.6	17.1	5.1	300
4	140/80	180/60	75	147	53	70	45	63	109	113	51	34	58	79	4.3	11.3	5.6	300
5	120/80	140/80	75	143	50	67	39	44	182	127	91	42	91	85	7.1	11.7	4.0	300
6	140/80	220/60	60	160	45	61	26	39	187	160	103	63	84	98	5.3	14.6	6.7	400
7	160/80	190/80	120	167	60	63	53	60	88	89	35	33	53	57	6.5	9.2	2.1	200
8	120/80	190/70	62	150	51	62	27	36	135	119	66	45	69	74	4.7	11.0	4.5	300
9	110/80	150/70	83	157	55	69	36	42	82	107	37	30	45	74	3.7	11.3	7.0	400
10	112/70	160/70	54	138	56	60	53	44	126	129	55	52	70	77	3.7	10.6	7.0	400
Mean	130/81	178/73	73	147	54	66	38	42	131	114	62	40	69	75	4.9	11.3	4.8	300
±SD	16/7	25/12	20	18	4	4	13	13	41	27	23	13	20	14	1.2	2.8	1.9	81

BP = blood pressure; CI = cardiac index; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; Ex = exercise duration; LVEF = left ventricular ejection fraction; R = rest; RVEF = right ventricular ejection fraction; SD = standard deviation; SVI = stroke volume index; Wrk = work load achieved.

Discussion

SCA is chronic hemolytic anemia with myriad clinical manifestations. The most common form of this hemoglobinopathy, hemoglobin SS, affects 1 in 500 black infants born in the United States.[17] Hemoglobin SS disease is a result of the homozygous expression of a mutant globin gene. (Valine replaces glutamic acid at the sixth position on the globin chain.) Deoxyhemoglobin S spontaneously polymerizes into fibers that cause the characteristic distortion and rigidity of the sickled cell. The vascular occlusion caused by these abnormal red cells accounts for many acute and chronic problems of SCA.

Retrospective analysis of autopsy data in 1973 suggested that the mortality rate, primarily due to overwhelming infection, was 20 to 30% in the first 5 years of life.[18] Survival beyond 40 years of age was uncommon. Today, better awareness of the disease and its potential complications have improved the outlook for affected persons.

Our study indicates that in mildly symptomatic adults with SCA, the LV function was normal or near normal at rest and during exercise, and that the LV perfusion pattern was also normal at rest. Thus, myocardial fibrosis secondary to coronary vaso-oclusive disease is not common. However, the LVEF was lower in patients with SCA than age-matched normal subjects both at rest and during exercise. Previous studies in patients at rest have also shown normal LV function.[19–21] In the study of Covitz et al,[21] the resting EF was <50% in only 2 of their 22 patients (9%), and an abnormal response to exercise was noted in 4 patients. In contrast, RV function was abnormal at rest and during exercise (or both) in most of our patients. RV function was abnormal in 7 of our 8 patients with clinically recognized RV dilation or a loud pulmonic component of the second heart sound.

Abnormal RV uptake of thallium-201 at rest suggests RV pressure or volume overload (or both).[22,23] Although RV volumes were not directly measured in our study, they must have increased, because the LV was dilated, the RVEF was lower than LVEF, and the stroke volume of both ventricles is the same in the absence of valvular regurgitation. LV dilation and high resting cardiac output seen in our study support previous findings.[7,11,12,19,20] Some possible reasons for RV dysfunction in our patients are pulmonary hypertension,

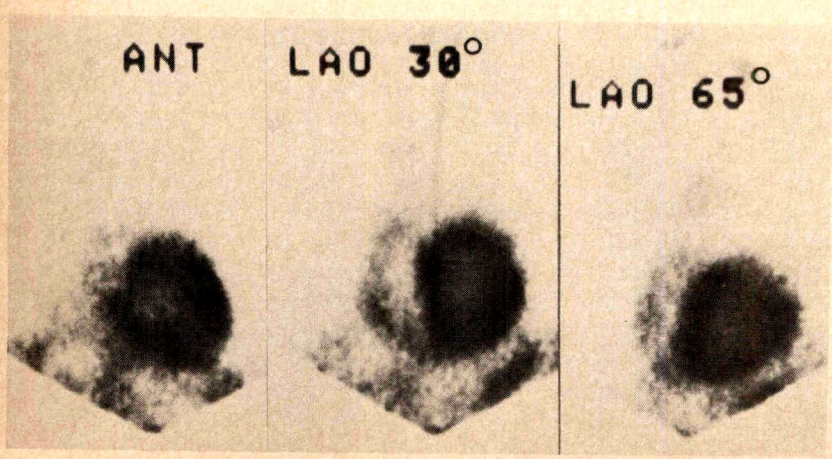

FIGURE 1. Resting thallium-201 image showing normal left ventricular perfusion and right ventricular uptake. ANT = anterior; LAO = left anterior oblique.

chronic volume overload, iron overload and coronary artery disease. None of the patients had evidence of coronary artery disease based on their age, history, exercise electrocardiographic response or exercise LV function. Whether chronic volume overload can produce isolated RV dysfunction is not known. A previous study[24] suggested that RV function was normal in patients with RV volume overload due to atrial septal defect. Pulmonary hypertension has been described in patients with SCA,[9,12] although it is unlikely to be due to LV dysfunction or chronic obstructive lung disease, since LV function was normal and there were no historical or clinical findings to suggest the diagnosis of chronic obstructive lung disease.

Thus, RV dysfunction in patients with SCA is most likely due to pulmonary hypertension secondary to repeated pulmonary infarctions. This finding is in agreement with the results of Korr et al,[24] who found a significant correlation between RVEF and pulmonary artery pressure. Confirmation of pulmonary hypertension by hemodynamic measurement would have been useful, but invasive studies in these patients were not justifiable. Considering the magnitude of the problem, the scarcity of exercise data, especially exercise ventricular function, is surprising. In our study and that of Covitz et al,[21] the exercise capacity was reduced despite the presence of a high cardiac output state, probably because of the decrease in the oxygen-carrying capacity of the blood.

The noninvasive nature of the radionuclide procedures used in this study offers a distinct advantage. Future investigators should consider the natural history of the disease relative ventricular function, especially with a view to ascertaining whether abnormal function can be detected and possibly corrected at an earlier stage of the disease.

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Effects of Negative Pleural Pressure on Left Ventricular Hemodynamics

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Negative pleural pressure alters left ventricular (LV) function. LV volume changes have been studied in human subjects, but little is known of the hemodynamic effects. The effect of changes of pleural pressure on LV hemodynamics during a Mueller maneuver (inspiration against an obstruction) was studied in 11 subjects and during quiet, unobstructed inspiration in 3. During the Mueller maneuver, there was an initial decrease in pulmonary wedge pressure and aortic systolic pressure, almost as great as the decrease in pleural pressure. Thereafter, these pressures increased despite a sustained reduction in pleural pressure. Toward the end of the Mueller maneuver, pulmonary wedge transmural pressure averaged 31 ± 12 mm Hg and in 6 patients large *v* waves developed. The increase in aortic transmural pressure averaged 30 ± 16 mm Hg. Aortic pulse pressure decreased on the first beat from control levels of 59 ± 21 to 47 ± 21 ($p < 0.001$) and then returned to control levels.

During normal breathing in 3 subjects, studied with intraesophageal balloons, there was a similar increase in both transmural aortic and transmural pulmonary wedge pressures with a decrease in pleural pressure 6 mm Hg during inspiration.

Thus, increased negative pleural pressure was associated with a marked increase in pulmonary wedge transmural pressure; the increase was approximately proportionate to the decrease in pleural pressure. It is suggested that this increase was due to increased impedance to LV ejection and to right ventricular expansion interfering with LV diastolic filling.

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Fluid accumulation in the lungs is enhanced by very negative pleural pressures[1] and negative pleural pressures are frequently seen in conditions with airway obstruction[2] as well as conditions with noncompliant lungs such as pulmonary edema.[3] The potential mechanism for this fluid accumulation has become clearer in the past few years. Negative pleural pressure affects left ventricular (LV) function by at least 2 mechanisms: It causes an increase in the venous return to the right side of the heart,[4] which results in increased right ventricular (RV) volume, a shift in the ventricular septum to the left,[5] and RV interference with LV function.[6–11] It also produces an impedance to LV ejection.[9–15] Both of these mechanisms lead to an increase in left atrial LA transmural pressure (that is, LA pressure relative to pleural pressure). This increases the pulmonary venous and capillary hydrostatic pressures, which, in turn, leads to greater fluid accumulation in the lungs.[1,2] The effects of a negative pleural pressure on LV volumes has been well studied,[14,15] but few data are available on the ventricular pressure changes in human subjects.[16] This study quantitates the increase in LA and aortic transmural pressure during an inspiratory effort to determine the potential magnitude of the hemodynamic effects of negative pleural pressure in human subjects.

Methods

The effects of the Mueller maneuver were observed in 7 men and 4 women, aged 39 to 66 years, during routine cardiac catheterization. Seven patients had coronary artery disease, 3 valvular disease and 1 dilated cardiomyopathy. The details of their hemodynamic findings are given in Table I. LA pressure was estimated from pulmonary wedge pressure determined by an end-hole 7Fr catheter inserted percutaneously into the femoral vein and advanced to the pulmonary wedge position. The P_W was compared with the LV end-diastolic pressure determined by a retrograde arterial catheterization. Changes in mouth pressure were used to estimate changes in pleural pressure. In a Mueller maneuver, there is no air flow; therefore, changes in mouth pressure closely reflect changes in alveolar pressure, which in turn reflect changes in pleural pressure.[10] A pressure manometer allowed the patient to see the extent of the pressure change. All pressures were measured with Statham strain-gauge transducers placed 5 cm above the table level.

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TABLE I Patient Data

Case	Age (yr)	Mean RAP (mm Hg)	Mean PAP (mm Hg)	Mean W (mm Hg)	LVEDP (mm Hg)	EF (%)	LV Grade	EDVI (ml/m²)	Diagnosis
1	49	7	. . .	26	15–25	75	1/4	55	CAD: 1 vessel
2	51	7	23	13	9–13	63	1/4	54	CAD: 2 vessel
3	50	7	21	20	20–26	14	4/4	103	CAD: 3 vessel and blocked graft
4	56	5	13	11	6–12	63	1/4	48	AI and mod AS
5	35	6	15	9	9–13	61	2/4	58	Cardiomyopathy
6	43	3	30	15	9–12	. . .	2/4	. . .	Mild AI and AS
7	47	9	25	21	6–20	61	2/4	101	CAD: 3 vessel
8	52	. . .	. . .	16	. . .	68	3/4	56	CAD: 2 vessel
9	66	3	18	12	10–12	68	2/4	66	CAD: complete left main obst.
10	53	11	25	26	6–9	>60	1/4	. . .	MS, MI mod; mild AI
11	39	5	13	8	11–14	78	2/4	89	CAD: single vessel

AI = aortic insufficiency; AS = aortic stenosis; CAD = coronary artery disease; EDVI = left ventricular end-diastolic volume index (normal = <98); EF = ejection fraction; LV = left ventricular (grade 1 = normal, 4 = severe dysfunction); LVEDP = left ventricular end-diastolic pressure; MI = mitral insufficiency; mod = moderate; MS = mitral stenosis; obst. = obstruction; PAP = pulmonary artery pressure; RAP = right atrial pressure; W = wedge pressure (except Case 4 with transseptal left atrial pressure).

Mueller maneuvers were performed by having patients inspire from end expiration (functional residual capacity) against a closed airway. After a number of practice sessions, a fairly constant negative pressure could be maintained for 8 to 15 seconds. Care was taken to avoid sucking with the cheeks and closing of the glottis. Patients were also instructed to avoid contracting their abdominal muscles, for this can elevate intraabdominal pressure and increase venous return. To study the changes during spontaneous respiration, an intraesophageal balloon was inserted to the level of the heart and filled with 0.5 ml of air in 3 patients (Cases 1, 2, and 3). Variations in intraesophageal balloon pressure, wedge pressure and aortic pressure were then studied during Mueller and normal respiration in the supine position. Similar results were found during the Mueller maneuver whether mouth or esophageal pressures were used.

Mean pulmonary wedge pressure was obtained by graphically integrating the phasic pressure; arterial pressure was measured at peak systole. The change in intrapleural pressure (P_{Pl}) with each maneuver was assumed to equal the change in mouth or esophageal balloon pressure. It was subtracted from the change in wedge (P_W) and aortic pressure (P_{Ao}) to calculate the net change in the transmural pressures (P_W-P_{Pl} and P_{Ao}-P_{Pl}). Similarly, changes in intraesophageal pressure during respiration were used to calculate changes in net transmural wedge and aortic pressures. The values during the first beat, the middle and end of the Mueller maneuvers were compared with the resting values by a paired Student *t* test. For respiration, the changes in intrapleural, wedge and aortic pressures from peak inspiration to expiration from 14 to 35 respiratory cycles were analyzed. During systole, the LV transmural pressure is almost equal to the aortic transmural pressure; we assume for the purpose of this discussion that changes in one are equivalent to changes in the other. Thus, increase of aortic transmural pressure indicates increased impedence to LV ejection.

Results

A typical response to the Mueller maneuver with change in mouth pressure is shown in Figure 1 and a change in esophageal pressure in Figure 2. The average response of 11 subjects during control breathing and during early, middle, late and post-Mueller maneuvers are shown in Figure 3 and Table II. In all subjects there was an immediate decrease in the wedge and aortic pressures relative to atmospheric pressure. The wedge

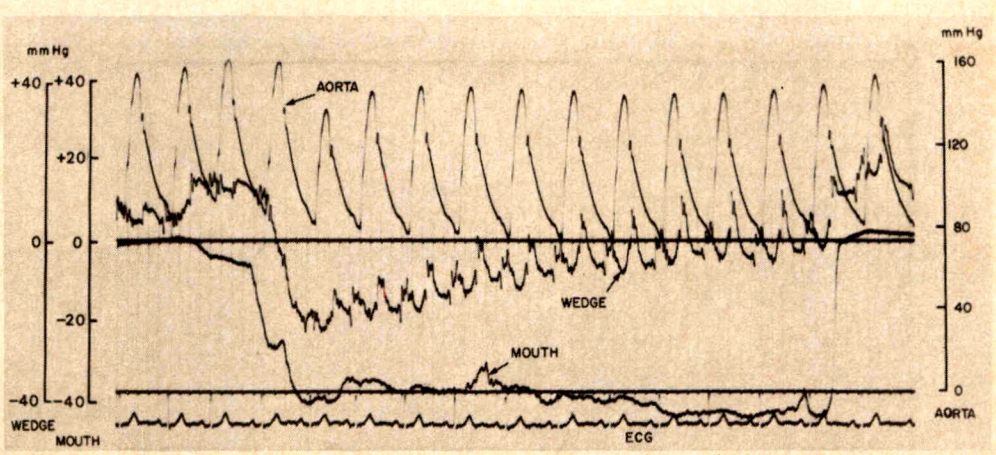

FIGURE 1. Aortic, (P_{Ao}) wedge (P_W) and mouth (P_M) pressures ($\Delta P_{pl} \simeq \Delta$ P mouth) during Mueller maneuver in Case 8. The **line in the center** is zero pressure for the mouth and wedge. With the abrupt decrease in P_M, the P_W decreased and then increased almost back to control levels. The P_{Ao} also decreased initially and then oscillated around the control pressure. Since the P_{Ao} and P_W did not decrease as much as P_M and increased further while P_M was constant, their transmural pressures increased considerably. Note the rebound in P_W on release of the Mueller maneuver. ECG = electrocardiogram.

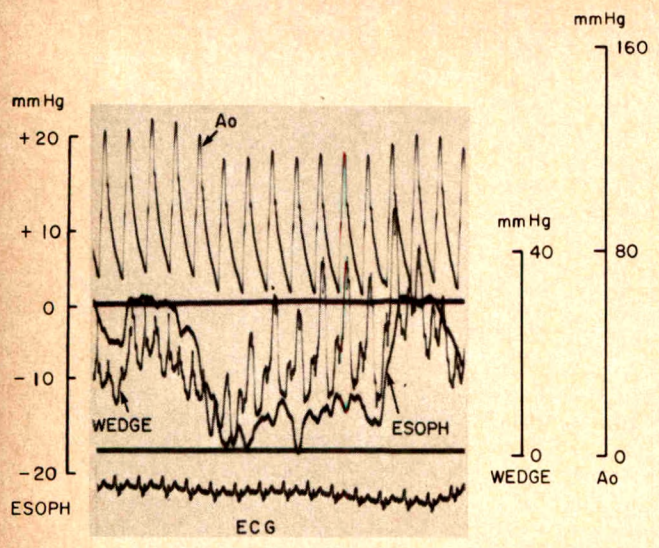

FIGURE 2. Aortic (Ao), wedge (WEDGE) and esophageal (ESOPH) pressures during Mueller maneuver in Case 3 demonstrating the development of large *v* waves.

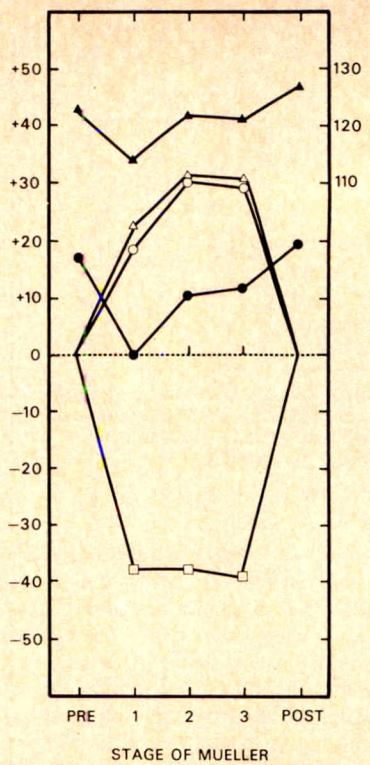

FIGURE 3. Mean changes in intraluminal mean left atrial, aortic (systolic) and transmural pressures (mm Hg) during Mueller maneuvers in 11 subjects. **Filled circles,** intraluminal left atrial pressure; **empty circles,** change in mean transmural left atrial pressure; **empty squares,** change in mouth pressure; **filled triangles,** intraluminal aortic systolic pressure; **empty triangles,** change in transmural aortic systolic pressure.

pressure then usually increased, but not back to the control level. The arterial pressure returned to near control levels or higher within 3 to 4 beats. With the onset of the Mueller maneuver, the decrease in pleural pressure was always greater than the decrease in wedge and aortic pressures, and therefore, the transmural pressures increased even on the first beat.

In Figure 4 the changes in LA transmural pressure as determined by pulmonary capillary wedge pressures are plotted against the changes in pleural pressure. Transmural pressure increased as a function of the decrease in pleural pressure and tended to be higher in the middle and late Mueller maneuvers than at the beginning of the maneuver. Only 2 patients at some point had no increase in transmural wedge pressure (Case 10, a woman with mitral stenosis and regurgitation and Case 4, a man with aortic regurgitation and stenosis).

The average changes in pulse pressure and RR interval during maneuvers are shown in Table II. Pulse pressure decreased immediately and then returned to control levels within 3 to 4 beats. There was an immediate shortening of the RR interval, with a return to control levels by the middle of the Mueller maneuver.

Large *v* waves developed in 6 subjects during the Mueller maneuver (Fig. 1 and 4). Two patients had valvular disease and small *v* waves at rest, whereas the other 4 had 3-vessel coronary artery disease and no mitral regurgitation on a subsequent left ventriculogram. The *v* waves tended to be more prominent during successive Mueller maneuvers.

TABLE II Hemodynamic Data

Data	Before Maneuver	Mueller Stages			After Maneuver
		1	2	3	
P_{La} (mean) (mm Hg)	17 ± 6 (19)	0 ± 12† (19)	10 ± 9† (18)	13 ± 7‡ (19)	20 ± 8 (19)
$\Delta(P_{La}-P_{pl})$ (mm Hg)	0	18 ± 14 (19)	31 ± 17 (15)	30 ± 16 (19)	0
P_{Ao} (systolic) (mm Hg)	133 ± 19 (18)	114 ± 19† (19)	127 ± 23† (13)	126 ± 21† (17)	132 ± 19 (19)
$\Delta(P_{Ao}-P_{pl})$ (mm Hg)	0	23 ± 16 (19)	31 ± 13 (15)	31 ± 12 (19)	0
RR (ms)	844 ± 131 (29)	800 ± 144† (29)	824 ± 109* (29)	846 ± 110 (29)	852 ± 118 (29)
Pulse pressure (mm Hg)	59 ± 21 (32)	47 ± 21† (32)	59 ± 21 (24)	58 ± 23 (29)	59 ± 21 (28)

* $p < 0.05$. † $p < 0.001$.
P_{Ao} = aortic pressure; P_{La} = left atrial pressures; P_{pl} = pleural pressure.

Figure 5 is an example of aortic wedge and intraesophageal balloon pressures during spontaneous respiration. The inspiratory decrease in intraesophageal pressure was greater than that in aortic and wedge pressures.

The relationship between P_{La}-P_{Pl} and P_{Ao}-P_{Pl} to P_{Pl} during inspiration are shown for Cases 1, 2 and 3 in Figure 6 and 7. While aortic and LA transmural pressures increased with increasingly negative pleural pressure, the increase was in each case somewhat less than the decrease in pleural pressure.

Discussion

As predicted, the decrease in pleural pressure with the Mueller maneuver and inspiration was associated with a decrease in LA pressures (as evident by pulmonary capillary wedge pressure) relative to the atmosphere, but an increase in LA transmural pressure, that is, LA intracavitary pressure minus pleural pressure. The overlying pericardium is considered to be a portion of the LA wall, and hence, LA transmural pressure re-

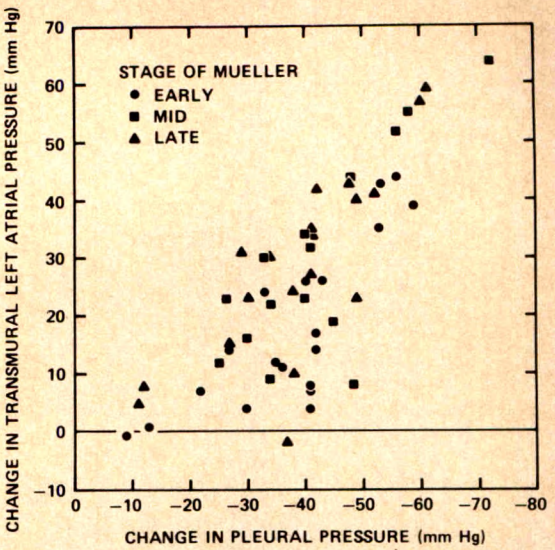

FIGURE 4. Changes in transmural left atrial pressure are plotted against changes in pleural pressure at 3 stages in the Mueller maneuver.

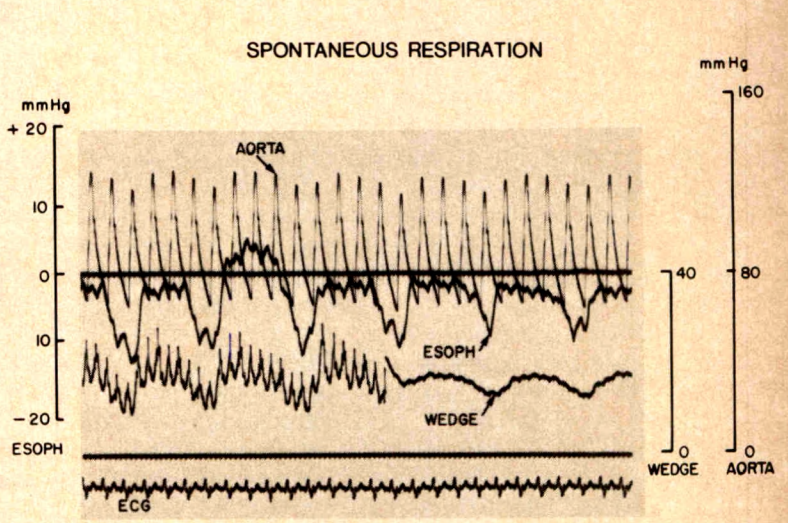

FIGURE 5. Aortic, wedge and esophageal pressures (pleural pressure) during normal respiration in the supine position for Case 1. Mean wedge pressure is also shown. Since the inspiratory decrease in pleural pressure was greater than the decrease in wedge and aortic pressure, the transmural aortic and left atrial pressures actually increased.

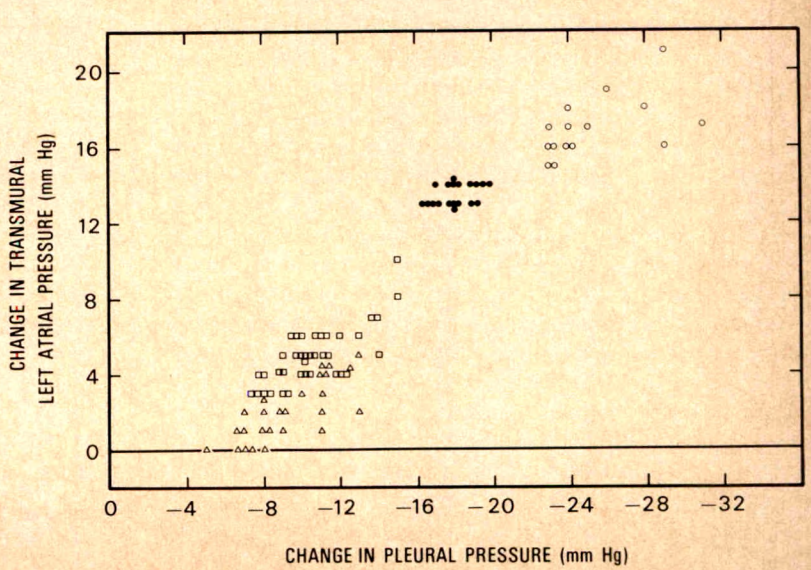

FIGURE 6. Changes in transmural left atrial pressure during inspiration in the supine posture are plotted against changes in pleural pressure for Cases 1 to 3. Patient 2 breathed with normal (**filled circles**) and deep inspiration (**empty circles**). **Triangles** represent Patient 1; **squares** represent Patient 3.

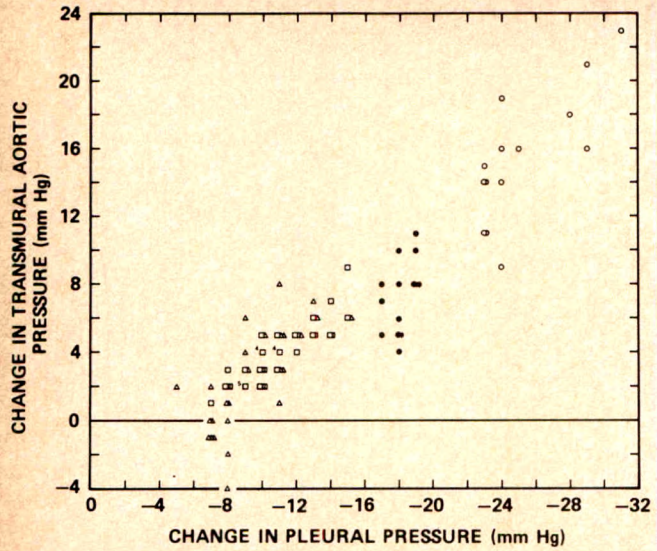

FIGURE 7. Changes in transmural aortic pressure during inspiration in the supine posture are plotted against changes in pleural pressure for Cases 1 to 3. Patient 2 breathed with normal (**filled circles**) and deep inspiration (**empty circles**).

flects the difference between pleural pressure and the LA cavity. With very negative pleural pressures, the LA transmural pressure increased to as high as 40 to 60 mm Hg. Thus, clinical conditions in which there are large swings in pleural pressure, such as tracheal obstruction or obstructive lung disease[2] or decreased lung compliance,[3] could cause large inspiratory increases in LA transmural pressure, which would in turn increase hydrostatic pressure at the pulmonary capillary level and potentially increase transudation of fluid.[1]

The dramatic rise in LA transmural pressure indicates that either the left-sided cardiac volume increased or the pressure-volume relation of the left heart shifted so that the same ventricular volume was associated with higher pressures.

The LV diastolic volume could be increased from the increase in LV afterload that develops with negative pleural pressure.[9–15] When pleural pressure decreases below atmospheric pressure, the left ventricle must overcome this negative pressure plus aortic pressure (during systolic ejection); thus, the left ventricle faces an increased afterload during ejection and end-diastolic volume will increase.[14] However, canine studies have shown that LA transmural pressure can increase during inspiration without an evident change in end-diastolic volume. One difference between the animal and human studies is that the negative pleural pressure was maintained constant in the human studies, and thus allowed time for volume adaptation to occur.[14] Furthermore, the heart is near its maximal volume in the supine position,[17] and therefore on the steep portion of its pressure volume curve; a small increase in ventricular volume could produce a large increase in transmural pressure. However, in addition to the increased afterload with negative pleural pressure, there is most likely a change in the pressure-volume relation of the left side of the heart from RV interference with LV function.[7–9] This change occurs because venous return to the right side of the heart increases with the decrease in pleural pressure and the increased RV volume thus increases RV interaction with the left side of the heart.[5–10]

Ventricular interaction cannot be the only explanation for the increase in LA transmural pressure for the pressure increased progressively during the Mueller maneuver, even though the pleural pressure did not change. It seems unlikely that the progressive increase in LA transmural pressure occurred because of a continuous increase in right heart volume. More likely, increased output from the right ventricle[18] reached the nearly maximally dilated left ventricle so that there was a large increase in LV diastolic pressure from a small increase in volume because the ventricle was on the steep portion of its pressure-volume curve.

The progressive increase in LA transmural pressure may also have been the result of a progressive increase in afterload, for after the first few beats the aortic pressure usually increased back to control levels despite sustained negative pleural pressure. Thus, there was further increase in LV afterload. As shown in Figure 3, the mean increase in LA pressure paralleled the mean increase in aortic transmural pressure.

The concept of transmural pressure applies when one is dealing with an elastic structure. When the heart is maximally dilated, it is effectively very stiff or inelastic. Thus, further decreases in pleural pressure will have little effect on the diastolic volumes, and the transmural pressure should increase in proportion to the decrease in pleural pressure. This was the case at the most negative pleural pressures (Fig. 3).

There was always a reduction in pulse pressure in the first few beats during the Mueller maneuver, which implies that stroke volume decreased, as is known to occur during inspiration.[18–20] Pulse pressure returned to normal by the midportion of the Mueller maneuver, suggesting either reflex changes in cardiac contractility or maintenance of output by higher end-diastolic volumes. The decrease in stroke volume is best explained by the RV interference with LV function[6–11] and by negative pleural pressure acting as an impedance to LV ejection[9–15] as discussed previously. The older belief that the inspiratory decrease in stroke volume is a result of pooling of blood in the lungs,[18,19,21] and thus decreased ventricular filling, is unlikely, considering the very large increase in LA transmural pressure[10,20] and the demonstration that end-diastolic volume does not decrease during inspiration.[13–15]

There are several possible explanations for the large *v* waves that developed during the Mueller maneuver. The increased LV afterload could have increased preexisting mitral regurgitation, which was known to be present in 2 subjects and increased LV volume might have caused mitral regurgitation in the others. The rapidity with which regurgitation developed and disappeared makes transient papillary muscle ischemia an unlikely cause. Alternatively, the large *v* waves could have been due to increased LA filling and not mitral regurgitation.

The decrease in pleural pressure with normal respiration produced a similar pattern of change in LA

transmural and aortic transmural pressures, as seen during the Mueller maneuver (Fig. 6 and 7). In addition to the mechanisms discussed, during normal inspiration lung inflation adds on impedance to RV ejection,[22,23] which would further increase RV volume on inspiration and exaggerate RV interference with LV function.

In the clinical setting, the relative role played by increased RV volume and increased LV afterload during negative pleural pressure varies with the circumstances. LV afterload is increased in direct proportion to the extent and duration of the decrease in pleural pressure during inspiration.[24] Because the decrease in stroke volume for any given increase in afterload varies with the status of the LV muscle, inspiratory impedance to LV emptying will cause greater reduction in stroke volume when LV function is depressed. The role of mechanical coupling will be greater when the venous pressure is elevated, because inspiration will cause a greater increase in venous return for any given decrease in pleural pressure. Similarly, pericardial effusion or rapid increase in heart size will tend to increase pericardial tension and also enhance the mechanical coupling between the right and left ventricles.

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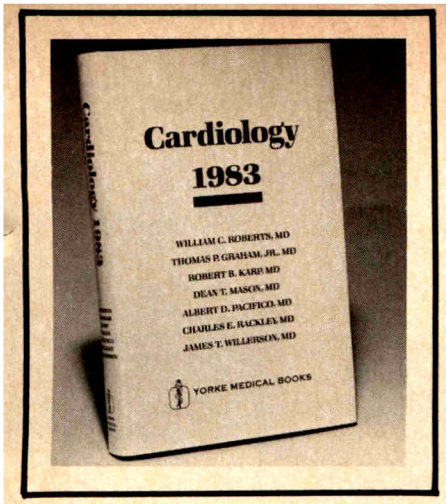

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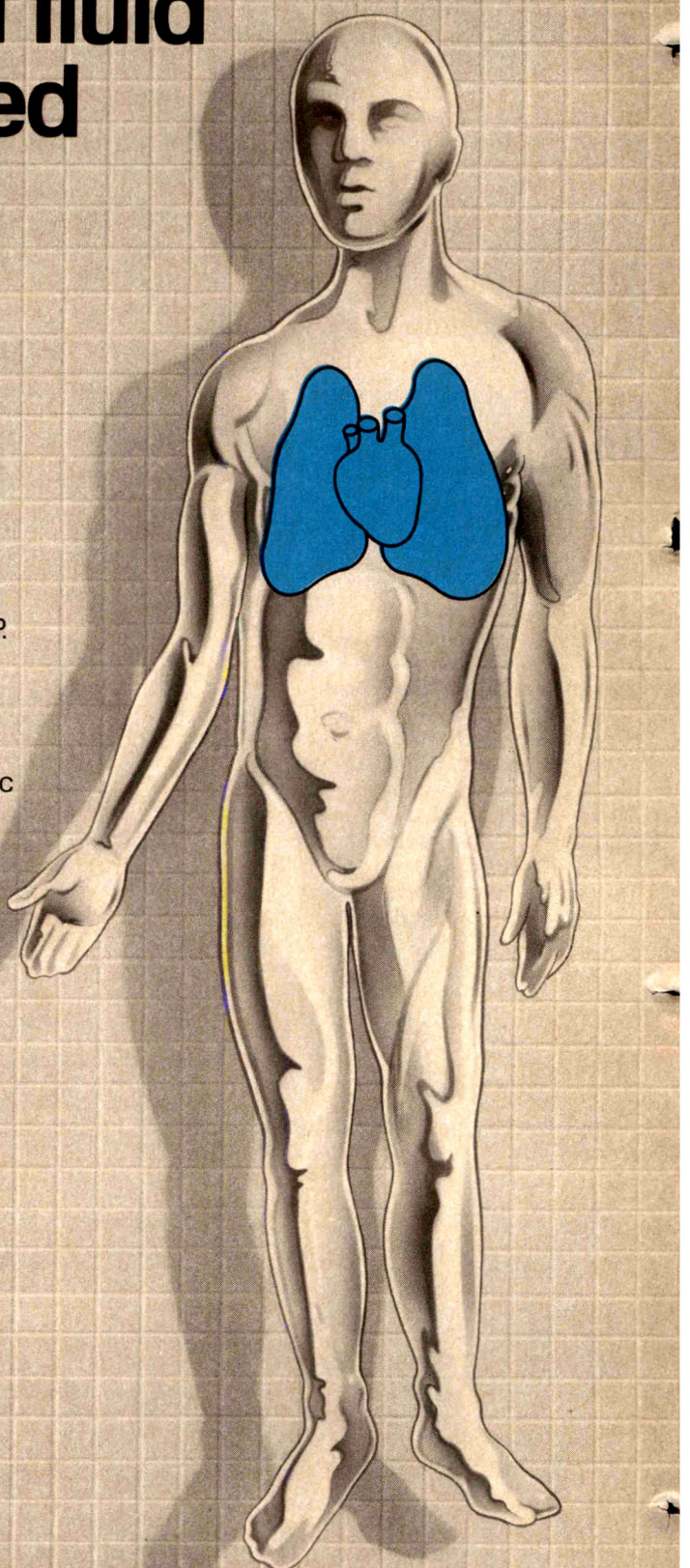
Therapeutic challenge:

Redistribution of fluid in CHF associated with acute MI



In Early CHF[1]

Pulmonary congestion with increased preload.

Findings: Elevated preload, elevated blood pressure, normal or slightly decreased cardiac output; PCWP greater than or equal to 18 mm Hg.

Therapeutic goal:
Reduce pulmonary congestion, lower PCWP to 15 to 18 mm Hg.

In Late CHF[1]

Pulmonary congestion with increased preload and afterload.

Findings: Low cardiac output, depressed blood pressure, and high PCWP.

Therapeutic goal:
Reduce pulmonary congestion, preload, and afterload, increase cardiac output, and lower PCWP to 15 to 18 mm Hg.

Why wait for the patient to become unresponsive to traditional diuretic/digitalis therapy?

1. Forrester JS, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;295:1356-1362, 1404-1413.

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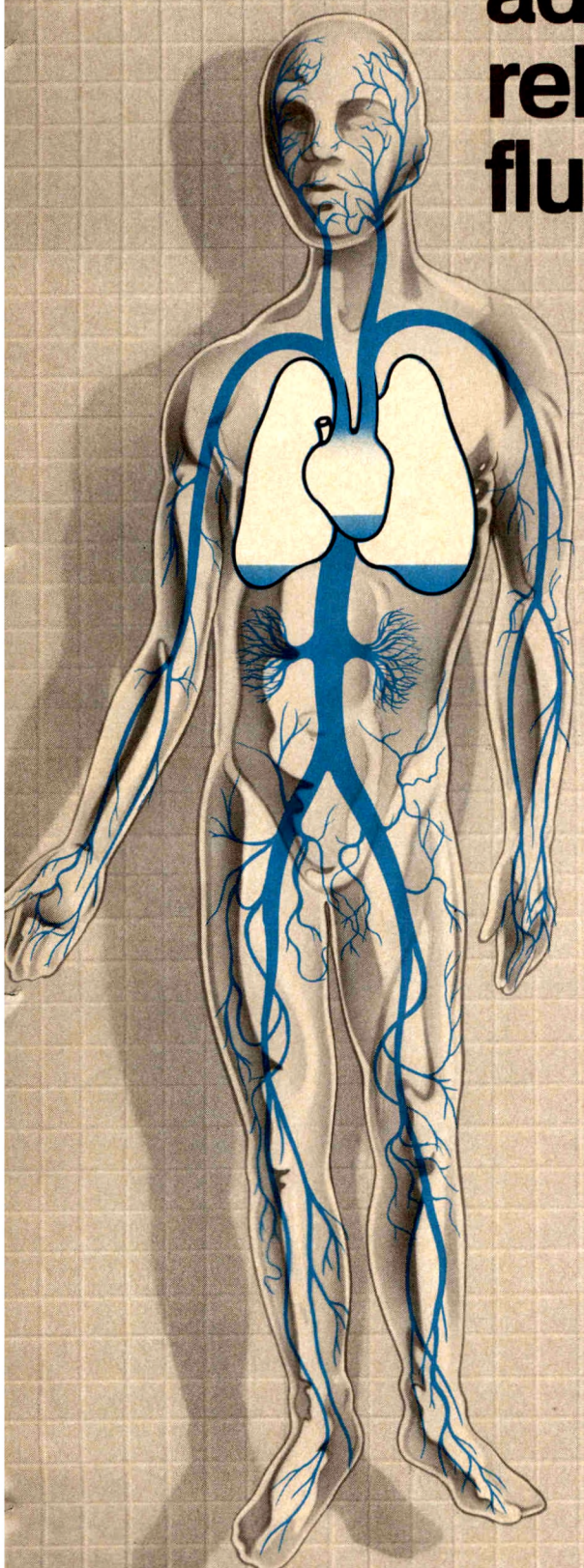

In a dose-related manner, Tridil produces dilation of both arterial and venous beds—for a therapeutic redistribution of fluid.

Suggested therapy in early CHF

If blood pressure is normal:
Tridil to reduce preload and PCWP. Diuretics to decrease fluid volume.

If blood pressure is elevated:
Tridil should be initiated immediately to decrease preload, PCWP, and blood pressure, while maintaining coronary perfusion.

Suggested therapy in late CHF

If blood pressure is normal or only moderately depressed:
Vasopressors and Tridil adjunctively, with continuous hemodynamic monitoring.

If blood pressure is significantly depressed:
Vasopressors and Tridil adjunctively to reduce preload, afterload, and PCWP. Dopamine to increase the contractility of the myocardium. PCWP should be monitored.

Use of nonabsorbing Tridilset®

Sorptive loss of Tridil may range up to 80% when infused through a conventional PVC administration set[2] To overcome this problem, administer Tridil through Tridilset administration set or Tridilset V.I.P.™ volumetric pump connector set.

The most frequent adverse reaction in patients treated with Tridil is headache. Please see the following page for a brief summary of prescribing information. Note: Tridil is a potent drug and must be diluted before infusion.

For additional information, contact the Medical Services Department, American Critical Care, division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, IL 60085, Phone 312/473-3000.

2. Baaske DM, et al: Administration set suitable for use with intravenous nitroglycerin. *Am J Hosp Pharm* 1982;39:121-122.

TRIDIL® (nitroglycerin) SYSTEM

American Critical Care

TRIDIL® (nitroglycerin)

Brief Summary of Full Prescribing Information

NOT FOR DIRECT INTRAVENOUS INJECTION. TRIDIL® MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION OF FULL PRESCRIBING INFORMATION). THE ADMINISTRATION SET USED FOR INFUSION WILL AFFECT THE AMOUNT OF TRIDIL DELIVERED TO THE PATIENT. (SEE WARNINGS, AND DOSAGE AND ADMINISTRATION SECTIONS.)

CAUTION

SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

CONTRAINDICATIONS

TRIDIL should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of TRIDIL in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

1. Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution and storage of TRIDIL for intravenous infusion should be made only in *glass* parenteral solution bottles.
2. Some filters absorb nitroglycerin; they should be avoided.
3. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinyl chloride (PVC) tubing of the intravenous administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest) the loss is neither constant nor self-limiting; consequently no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

Because of this problem, American Critical Care has developed TRIDILSET,® an administration set in which loss of TRIDIL is minimal (less than 1%). TRIDILSET (or a similar administration set) is recommended for infusions of TRIDIL.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN TRIDILSET IS USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF TRIDIL DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN TRIDILSET IS USED.

PRECAUTIONS

TRIDIL (nitroglycerin) should be used with caution in patients with severe liver or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of TRIDIL. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term studies in animals were performed to evaluate carcinogenic potential of TRIDIL.

Pregnancy

Category C. Animal reproduction studies have not been conducted with TRIDIL. It is also not known whether TRIDIL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TRIDIL should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRIDIL is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of TRIDIL in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with TRIDIL is headache, which occurs in approximately 2% of patients. Other adverse reactions occurring in less than 1% of patients are the following: tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness and abdominal pain.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

OVERDOSAGE

Accidental overdosage of TRIDIL may result in severe hypotension and reflex tachycardia which can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following TRIDIL administration is quite short, additional corrective measures are usually not required. However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (e.g., methoxamine or phenylephrine) should be considered.

DOSAGE AND ADMINISTRATION

(For complete information, please see Full Prescribing Information)

NOT FOR DIRECT INTRAVENOUS INJECTION

TRIDIL IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP OR SODIUM CHLORIDE (0.9%) INJECTION, USP PRIOR TO ITS INFUSION. TRIDIL SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Some patients with normal or low left ventricular filling pressures or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of TRIDIL and may respond fully to doses as small as 5 mcg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of TRIDIL. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g., blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate), MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

HOW SUPPLIED

NDC 0094-0090-05, 25 mg-5 ml ampul. NDC 0094-0090-10, 50 mg-10 ml ampul. Each ml contains 5 mg nitroglycerin. Protect from freezing.

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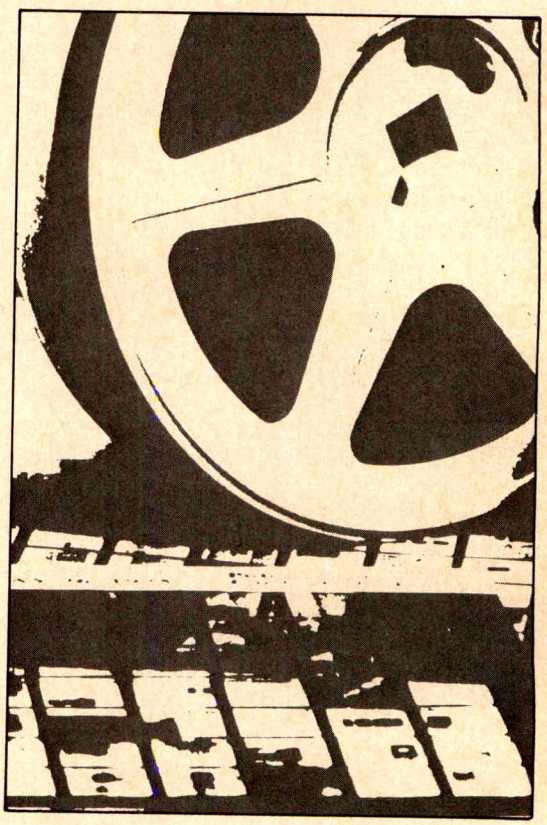

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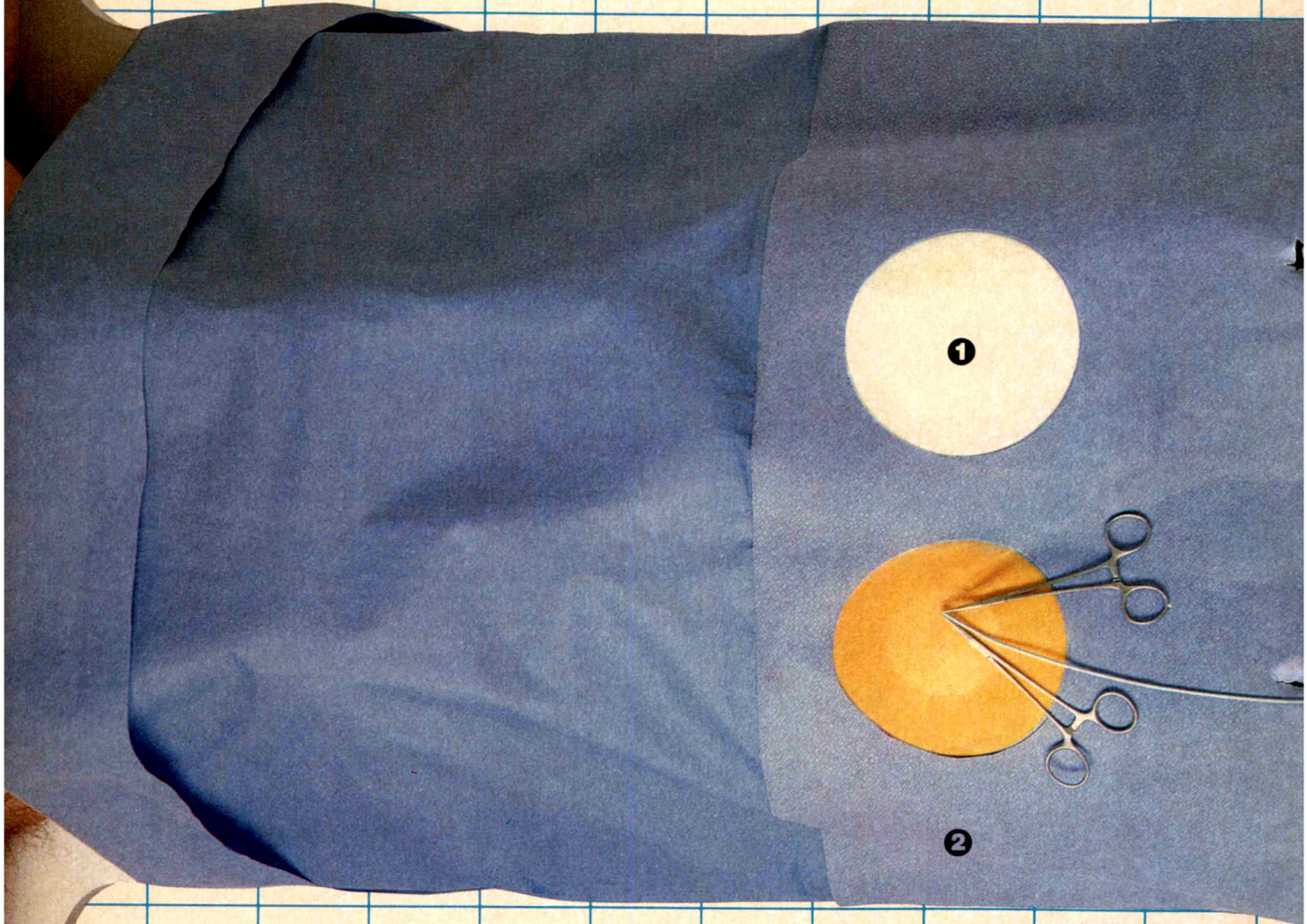

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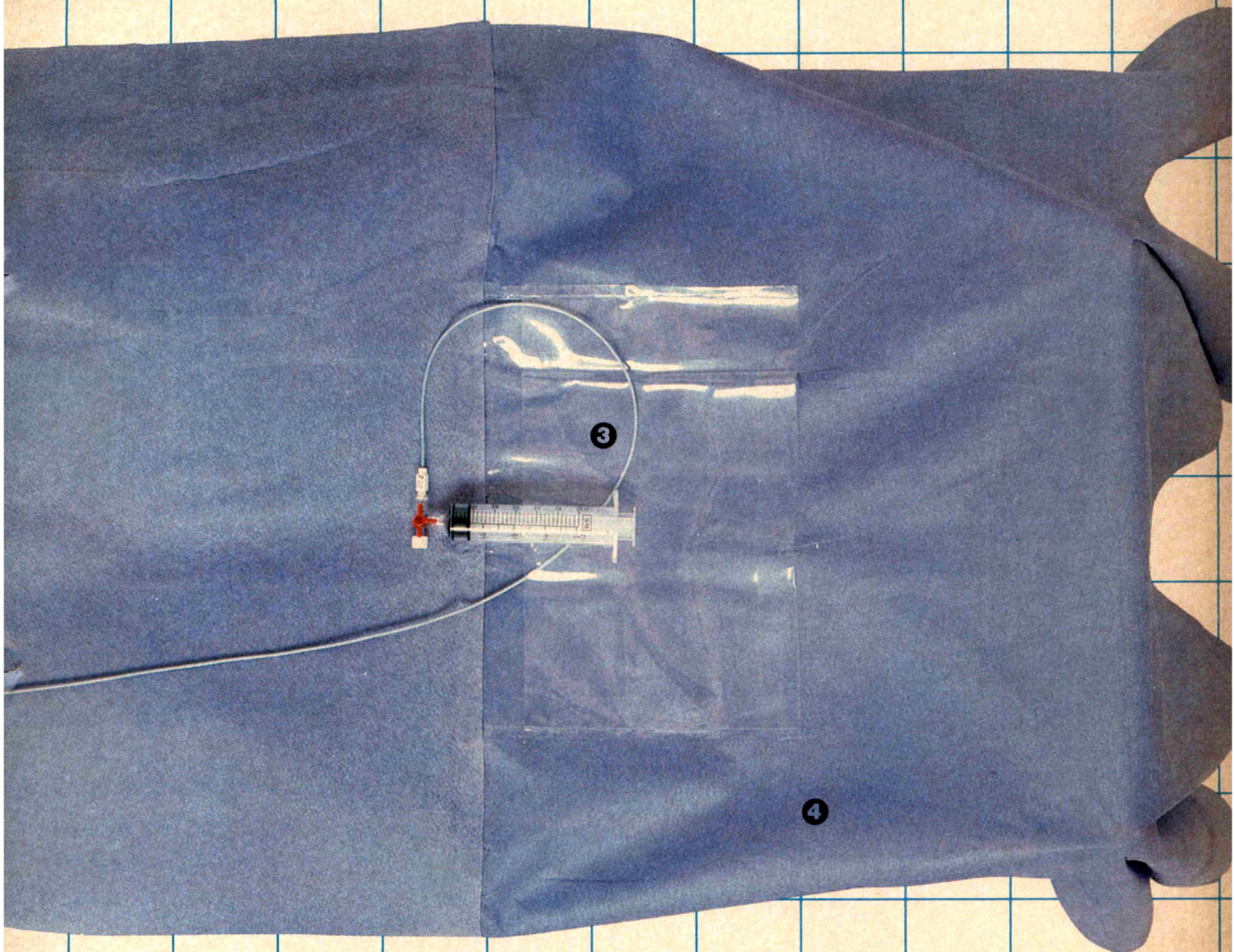

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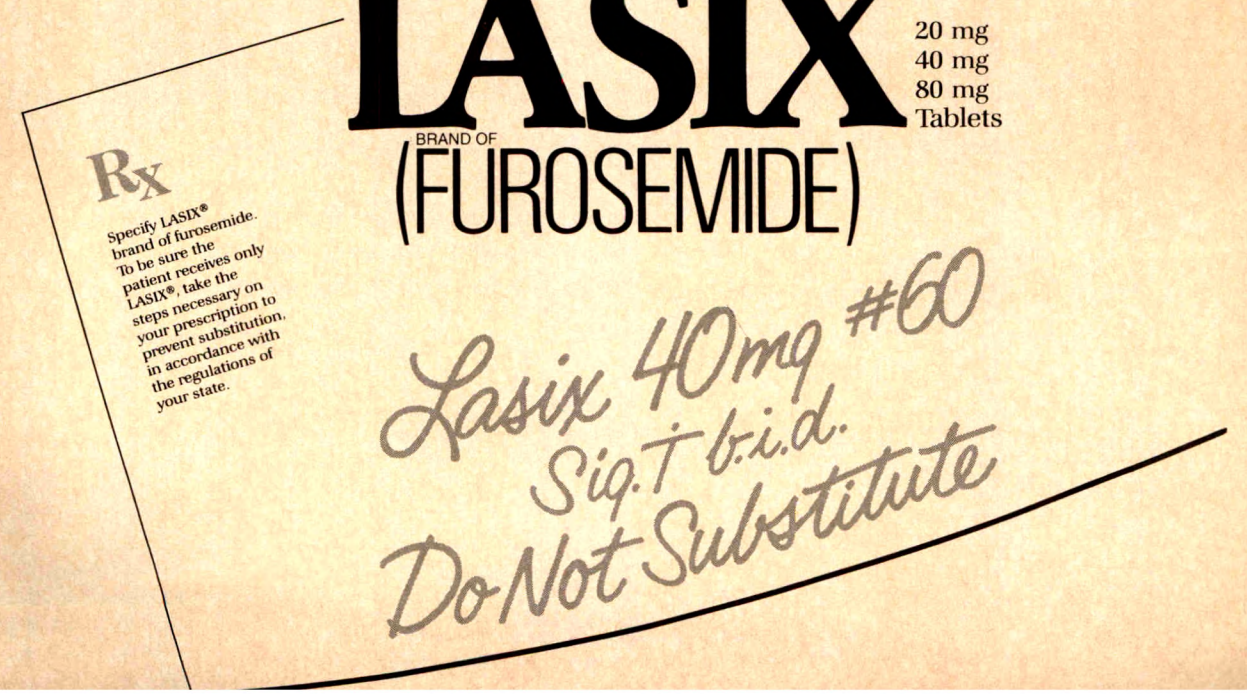

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions.

Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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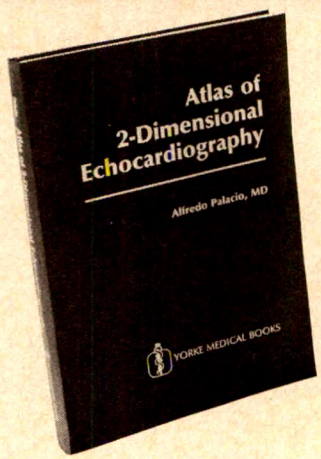
The First Practical Atlas of 2-D Echocardiography Ever Published



Atlas of 2-Dimensional Echocardiography

by Alfredo Palacio, MD
Director of National Institute of Cardiology, Guayaquil, Ecuador
Foreword by David H. Spodick, MD, DSc
Professor of Medicine, University of Massachusetts Medical School; Director, Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts

ISBN 0-914316-35-4, 198 pp, illus., large format 8¼ x 12, March '83, $65.00

2-dimensional echocardiography complemented by M-mode echocardiography has become one of the most common noninvasive diagnostic tools used by the cardiologist. With publication of the ATLAS OF 2-DIMENSIONAL ECHOCARDIOGRAPHY, neophyte and expert alike now have available to them the most truly usable didactic presentation of the subject ever published.

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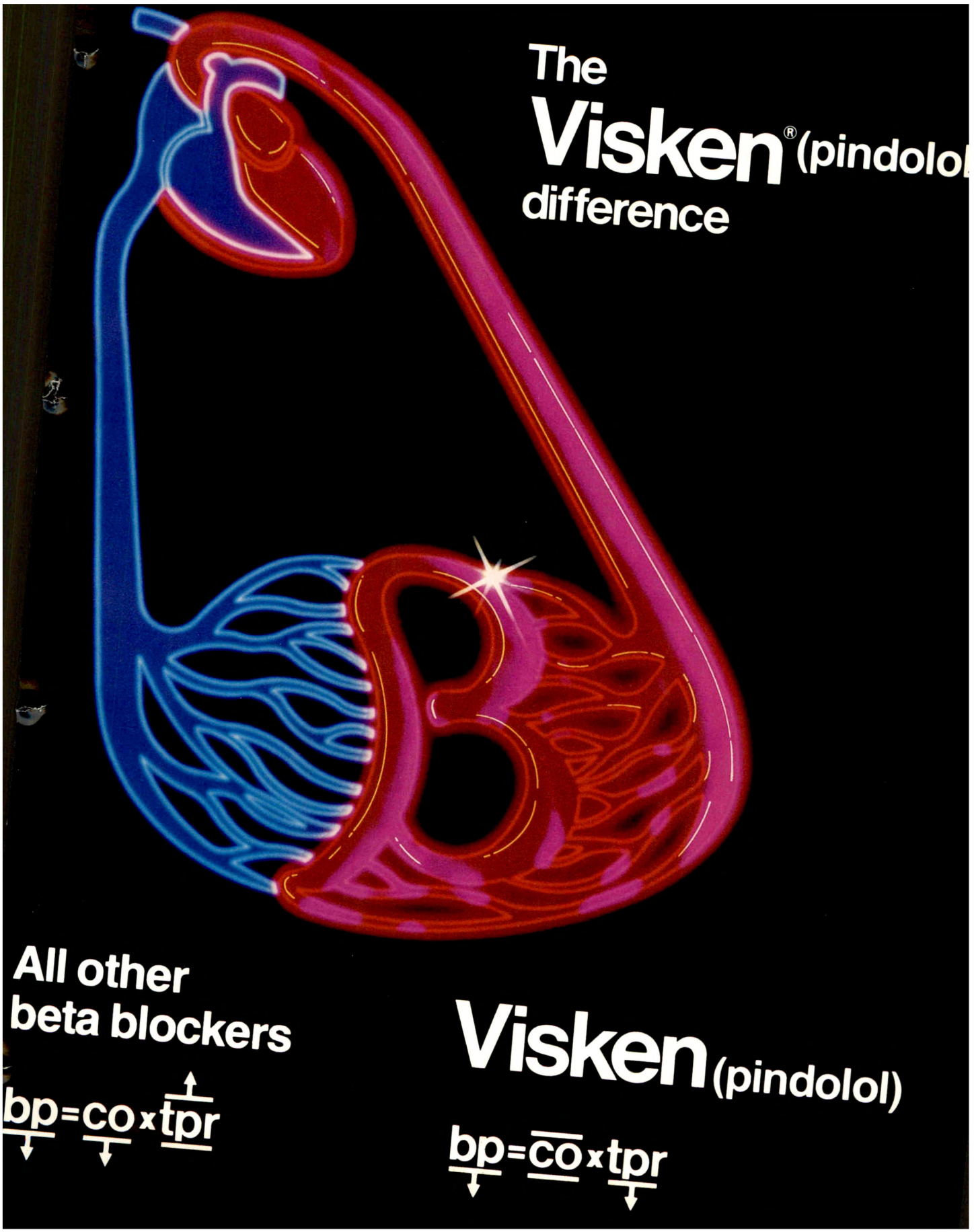
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beta blockers
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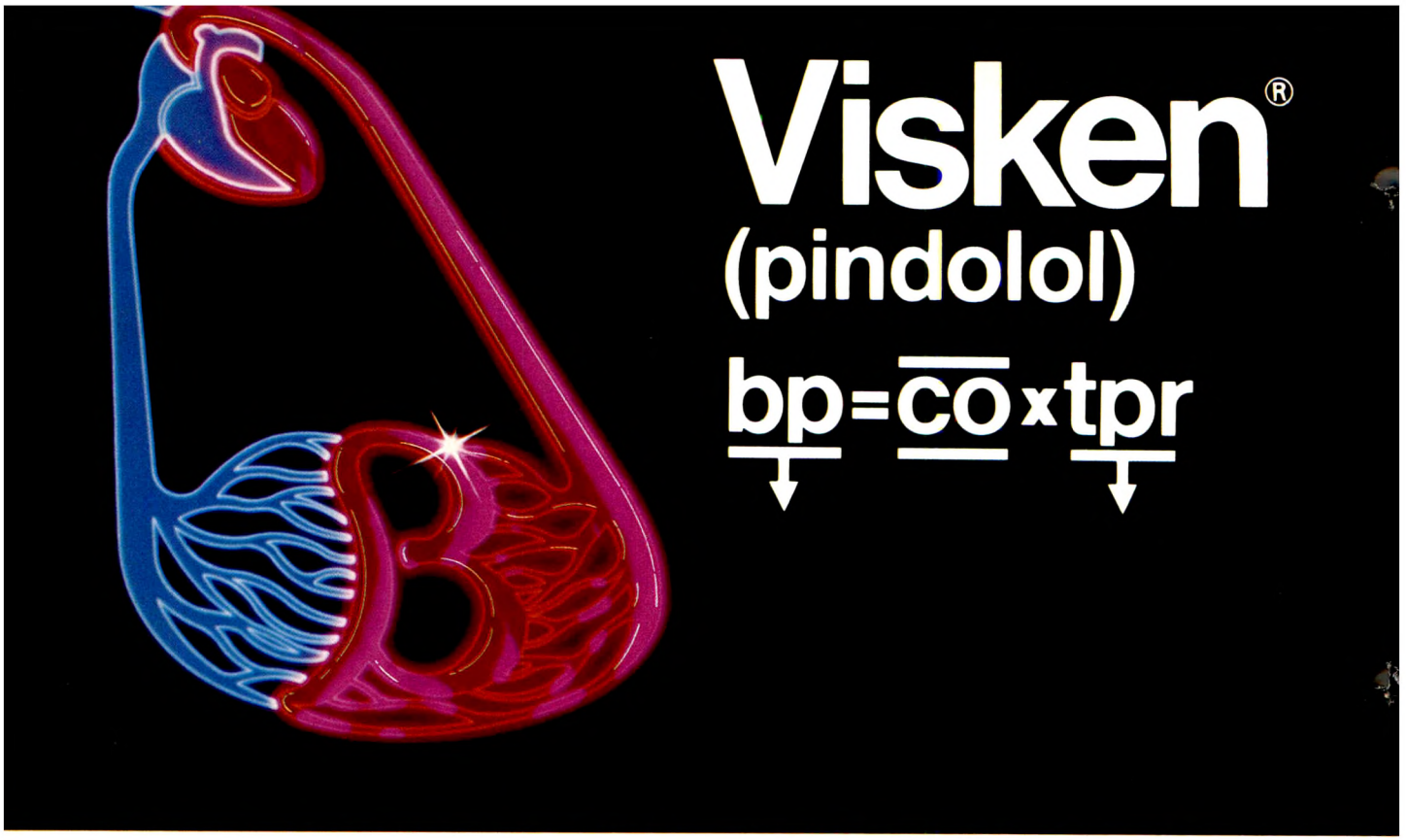

Makes hemodynamic sense in the treatment of hypertension

Reduces blood pressure

It's as effective as propranolol in normalizing blood pressure (dbp ≤ 90 mmHg) when used alone. It's also effective when used in combination with a diuretic.[1]

Has little effect on resting cardiac output

Unlike other beta blockers, Visken (pindolol) maintains resting cardiac output during long-term therapy. The clinical significance of this has not been evaluated.

Reduces total peripheral resistance*

Visken (pindolol) reduces one of the recognized components of hypertension: increased peripheral resistance.* Studies of 178 patients treated with Visken (pindolol) for at least two weeks have shown that Visken therapy reduces total peripheral resistance.[1]

Reduces exercise-induced tachycardia

Like other beta blockers, Visken (pindolol) blocks stimulation by catecholamines to reduce exercise-induced increases in systolic blood pressure and heart rate.

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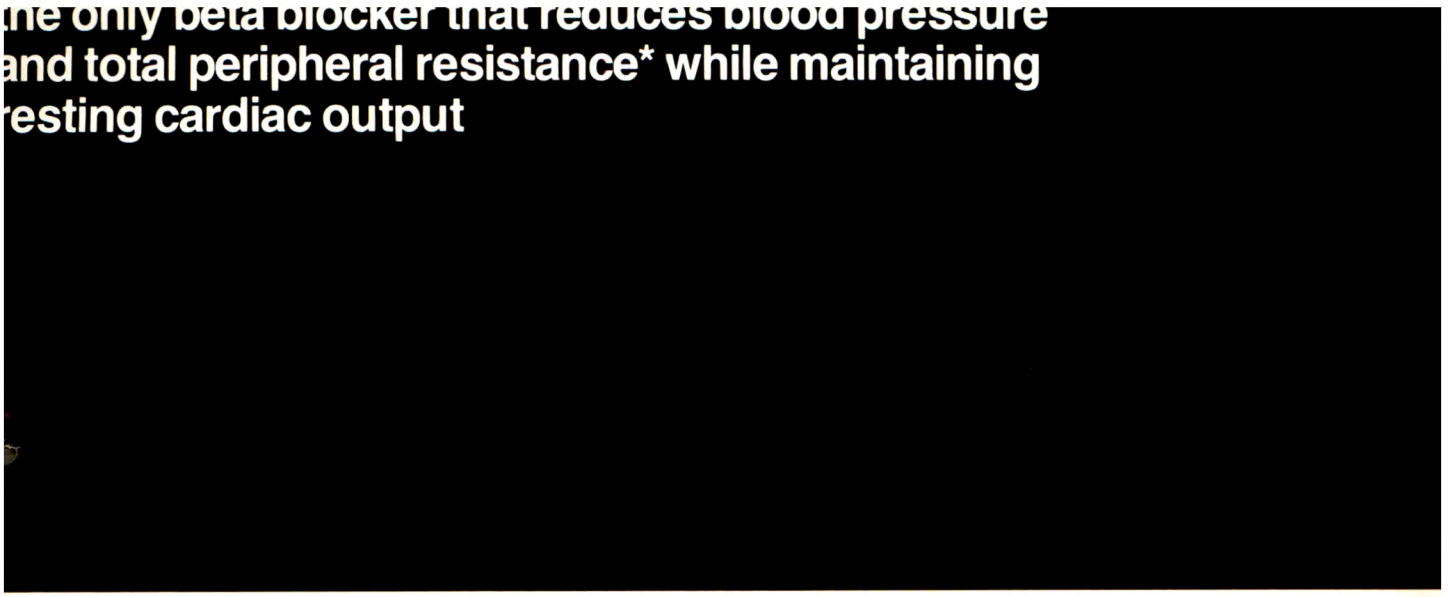
*The clinical significance has not been evaluated. See clinical significance statement on facing page of this advertisement.



Has little effect on resting heart rate

Visken® (pindolol) produces minimal changes in resting heart rate. Average reduction: 4-8 beats/minute.

The clinical significance has not been evaluated

The clinical significance of maintaining resting cardiac output, resting heart rate and reduced total peripheral resistance has not been evaluated and there is no evidence or reason to believe that exercise cardiac output is less affected by Visken (pindolol) than other beta blockers.

Maintains renal blood flow

Visken (pindolol) reduces supine and standing blood pressure while maintaining effective renal plasma flow and glomerular filtration rates.[2]

Favorable side effect profile

Low incidence of bradycardia

Low incidence of cold extremities

Visken (pindolol) is contraindicated in:

1) bronchial asthma
2) overt cardiac failure
3) cardiogenic shock
4) second- and third-degree heart block
5) severe bradycardia

*See clinical significance statement.

References:

1. Data on file, Sandoz Pharmaceuticals.
2. Wilcox CS, Lewis PS, Peart WS, et al: Renal function, body fluid volumes, renin, aldosterone, and noradrenaline during treatment of hypertension with pindolol. *J Cardiovasc Pharmacol* 3:598-611, 1981.

Please see next page of this advertisement for brief summary of prescribing information.

Visken® (pindolol)

The recommended initial dose of Visken (pindolol) is 5 mg b.i.d.

Many patients respond to 10 to 30 mg a day. The maximum dose is 60 mg per day. Dosage should be titrated on an individual basis. Available in 5 mg and 10 mg tablets.

Before prescribing or administering, see package circular for full product information. The following is a brief summary.

INDICATIONS AND USAGE
Visken (pindolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide type diuretic.

CONTRAINDICATIONS
Visken (pindolol) is contraindicated in: 1) bronchial asthma; 2) overt cardiac failure; 3) cardiogenic shock; 4) second and third degree heart block; 5) severe bradycardia; (see Warnings).

WARNINGS
Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, Visken (pindolol) can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without A History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Visken (pindolol) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Visken (pindolol), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Visken (pindolol) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Visken (pindolol) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—Patients with Bronchospastic Diseases Should in General Not Receive Beta-Blockers: Visken (pindolol) should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of Visken® (pindolol) can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid crisis.

PRECAUTIONS
Impaired Renal or Hepatic Function: Beta-blocking agents should be used with caution in patients with impaired hepatic or renal function. Poor renal function has only minor effects on Visken (pindolol) clearance, but poor hepatic function may cause blood levels of Visken (pindolol) to increase substantially.

Information for Patients: Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of Visken (pindolol) therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients receiving Visken (pindolol) plus a catecholamine depleting agent should, therefore, be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Visken (pindolol) has been used with a variety of antihypertensive agents, including hydrochlorothiazide, hydralazine, and guanethidine without unexpected adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In chronic oral toxicologic studies (one to two years) in mice, rats, and dogs, Visken (pindolol) did not produce any significant toxic effects. In two-year oral carcinogenicity studies in rats and mice in doses as high as 59 mg/kg/day and 124 mg/kg/day (50 and 100 times the maximum recommended human dose), respectively, Visken (pindolol) did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, Visken (pindolol) caused no adverse effects at a dose of 10 mg/kg.

In the male fertility and general reproductive performance test in rats, definite toxicity characterized by mortality and decreased weight gain was observed in the group given 100 mg/kg/day. At 30 mg/kg/day, decreased mating was associated with testicular atrophy and/or decreased spermatogenesis. This response is not clearly drug related, however, as there was no dose response relationship within this experiment and no similar effect on testes of rats administered Visken (pindolol) as a dietary admixture for 104 weeks. There appeared to be an increase in prenatal mortality in males given 100 mg/kg but development of offspring was not impaired.

In females administered Visken (pindolol) prior to mating through day 21 of lactation, mating behavior was decreased at 100 mg/kg and 30 mg/kg. At these dosages there also was increased mortality of offspring. Prenatal mortality was increased at 10 mg/kg but there was not a clear dose response relationship in this experiment. There was an increased resorption rate at 100 mg/kg observed in females necropsied on the 15th day of gestation.

Pregnancy—Category B: Studies in rats and rabbits exceeding 100 times the maximum recommended human doses, revealed no embryotoxicity or teratogenicity. Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, Visken (pindolol), as with any drug, should be employed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Visken (pindolol) is secreted in human milk, nursing should not be undertaken by mothers receiving the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

CLINICAL LABORATORY
Minor persistent elevations in serum transaminases (SGOT, SGPT) have been noted in 7% of patients during Visken (pindolol) administration, but progressive elevations were not observed and liver injury has not been reported in the medical literature over a ten (10) year period of marketing. Alkaline phosphatase, lactic acid dehydrogenase (LDH) and uric acid are also elevated on rare occasions. The significance of these findings is unknown.

ADVERSE REACTIONS
Most adverse reactions have been mild. The incidences listed in the following table are derived from 12 week comparative double-blind, parallel design trials in hypertensive patients given Visken (pindolol) as monotherapy, given various active control drugs as monotherapy, or given placebo. Data for Visken (pindolol) and the positive controls were pooled from several trials because no striking differences were seen in the individual studies, with one exception. The frequency of edema was noticeably higher in positive control trials (16% Visken (pindolol) vs 9% positive control) than in placebo controlled trials (6% Visken (pindolol) vs 3% placebo). The table includes adverse reactions reported in greater than 2% of Visken (pindolol) patients and other selected important reactions.

Body System/ Adverse Reaction	Total (Volunteered and Elicited) Visken (pindolol) (N = 322) %	Active Controls* (N = 188) %	Placebo (N = 78) %
Central Nervous System			
Anxiety	4	<1	1
Bizarre or Many Dreams	8	3	8
Dizziness	17	23	8
Fatigue	15	19	12
Hallucinations	1	0	0
Insomnia	19	8	12
Lethargy	3	6	4
Nervousness	11	5	9
Weakness	7	5	4
Autonomic Nervous System			
Paresthesia	5	2	8
Visual Disturbances	4	3	4
Cardiovascular			
Dyspnea	9	8	9
Edema	11	9	3
Heart Failure	2	<1	0
Palpitations	2	2	0
Weight Gain	3	5	0
Musculo-Skeletal			
Chest Pain	5	3	5
Joint Pain	11	6	8
Muscle Cramps	8	2	0
Muscle Pain	12	12	9
Gastrointestinal			
Abdominal Discomfort	7	7	5
Nausea	7	4	1
Skin			
Pruritus	2	<1	0
Rash	2	3	3

*Active Controls: Patients received either propranolol, α-methyldopa or a diuretic (hydrochlorothiazide or chlorthalidone).

The following selected (potentially important) adverse reactions were seen in 2% or fewer patients and their relationship to Visken (pindolol) is uncertain. AUTONOMIC NERVOUS SYSTEM: hyperhidrosis; CARDIOVASCULAR: bradycardia, claudication, cold extremities, heart block, hypotension, syncope, tachycardia; GASTROINTESTINAL: diarrhea, vomiting; RESPIRATORY: wheezing; UROGENITAL: impotence, pollakiuria; MISCELLANEOUS: eye discomfort or burning eyes.

POTENTIAL ADVERSE EFFECTS
In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of Visken (pindolol).

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block. See CONTRAINDICATIONS.

Allergic: Erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic and non-thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

Miscellaneous: Reversible alopecia; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with Visken (pindolol) during investigational use and extensive foreign experience amounting to over 4 million patient-years.

OVERDOSAGE
No specific information on emergency treatment of overdosage is available. Therefore, on the basis of the pharmacologic actions of Visken (pindolol), the following general measures should be employed as appropriate in addition to gastric lavage:

Excessive Bradycardia: administer atropine; if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: digitalize the patient and/or administer diuretic. It has been reported that glucagon may be useful in this situation.

Hypotension: administer vasopressors, e.g., epinephrine or levarterenol, with serial monitoring of blood pressure. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm: administer a $beta_2$ stimulating agent such as isoproterenol and/or a theophylline derivative.

A case of an acute overdosage has been reported with an intake of 500 mg of Visken (pindolol) by a hypertensive patient. Blood pressure increased and heart rate was ≥80 beat/min. Recovery was uneventful. In another case 250 mg of Visken (pindolol) was taken with 150 mg diazepam and 50 mg nitrazepam, producing coma and hypotension. The patient recovered in 24 hours.

DOSAGE AND ADMINISTRATION
The dosage of Visken (pindolol) should be individualized. The recommended initial dose of Visken (pindolol) is 5 mg b.i.d. alone or in combination with other antihypertensive agents. An antihypertensive response usually occurs within the first week of treatment. Maximal response, however, may take as long as or occasionally longer than two weeks. If a satisfactory reduction in blood pressure does not occur within 3-4 weeks, the dose may be adjusted in increments of 10 mg per day at these intervals up to a maximum of 60 mg per day.

HOW SUPPLIED
White, round, scored tablets: 5 mg and 10 mg, packages of 100. 5 mg tablets embossed "VISKEN 5" on one side, and "78-111" and scored on other side (NDC 0078-0111-05). 10 mg tablets embossed "VISKEN 10" on one side, and "78-73" and scored on other side (NDC 0078-0073-05).

[VIS-Z3 6/15/83]

SANDOZ PHARMACEUTICALS
DIVISION OF SANDOZ INC
EAST HANOVER, N.J. 07936

VIS-783-3

Effects of Posture and Respiration on Body Surface Electrocardiogram

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C. ANNE SPENCER, BSc, C. SUSAN ARMSTRONG, MSc,
B. MILAN HORACEK, PhD, and TERRENCE J. MONTAGUE, MD,
With the technical assistance of SHARON A. BLACK, RN, *and* SUSAN M. RIGBY, RN

To define more fully the effects of posture and respiration on electrocardiographic (ECG) patterns, 120-lead body surface potential maps (BSPM) were recorded in 36 normal subjects (aged 21 to 48 years) during cyclic respiration in both supine and upright positions; and at static end-tidal inspiration, functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV). In addition, BSPMs were recorded at TLC and RV during the Valsalva and Müller maneuvers, respectively. P-wave, QRS and ST-segment time integrals were evaluated. From supine to upright position, there was an inferior torso shift of P-wave and QRS distributions, but no change in amplitude of their maximal or minimal values; ST-segment distributions were spatially unaltered, but there was a significant ($p < 0.01$) decrease in the maximal value. Relative to maps during cyclic respiration in the upright position, maps at end-tidal respiration were similar; maps at TLC, however, displayed an inferior displacement of P-wave and QRS distributions and a decrease of QRS maximal and minimal values ($p < 0.01$). Valsalva and Müller maneuvers were not associated with marked changes in the appearances of BSPMs. The magnitude of variability, as assessed by a root-mean-square index, was greatest between maps recorded at TLC and RV; the least variability occurred between maps recorded at end-tidal inspiration and FRC. The variability between maps recorded in the supine and upright positions was intermediate. When root-mean-square variability data of all interventions were normalized by dividing by the respective mean data range (maximum minus minimum) of each time integral, the variability of P wave > ST segment > QRS ($p < 0.01$).

Thus, resting tidal volume respiration has little effect on body surface ECG patterns in normal adults. However, large volume respiration and posture change may substantially alter ECG body surface distributions and should be considered in states involving either factor.

(Am J Cardiol 1983;52:595–600)

Because it can reflect most of the surface-available electrocardiographic (ECG) data, body surface potential mapping (BSPM) is a useful and increasingly used electrocardiographic technique.[1–10] The surface distributions and temporal variability of several ECG time integrals at supine rest during tidal volume respiration in normal adults[5] and the influence of respiration on QRS potentials in normal children[11] have been described. Comprehensive descriptions of the effects of posture change and respiration on various BSPM values have not, however, been heretofore available. These data are necessary to allow optimal analysis of the body surface ECG, particularly during dynamic physiologic states involving either posture or respiratory changes in association with other interventions. Consequently, this study was undertaken to provide a spatial and quantitative perspective of posture and respiration-associated effects on BSPM distributions.

From the Departments of Medicine and Physiology and Biophysics, Dalhousie University and the Victoria General Hospital, Halifax, Nova Scotia, Canada. This study was supported by grants from the Nova Scotia Heart Foundation, the Medical Research Council of Canada (PG-18) and the Dalhousie Medical Research Foundation, Halifax, Nova Scotia, Canada. Manuscript received March 14, 1983; revised manuscript received May 10, 1983, accepted May 16, 1983.

Address for reprints: Terrence J. Montague, MD, Department of Medicine, Division of Cardiology, Victoria General Hospital, Halifax, Nova Scotia, Canada, B3H 2Y9.

Methods

Patients: Fifty-one persons, 27 men and 24 women aged 21 to 49 years, were studied. All subjects had a normal cardiac history, physical examination, time-motion echocardiogram and 12-lead electrocardiogram. None were taking cardiac medications.

Data recording and processing: The system of recording the body surface ECG signals has previously been described.[4,5,10] Briefly, simultaneous 15-second ECG recordings were obtained from 117 torso and 3 limb electrode sites with Wilson's central terminal as reference (Fig. 1). Data were recorded in digital format with a sampling frequency of 500 samples/s/channel. Computer-based analysis rejected ectopic beats and artifacts and performed selective averaging of the ECG complexes from each lead. For this study, the averaged complexes were placed on a baseline determined with a straight line from P onset to T offset, that is, a P-T baseline. Off-line editing of the 120-lead averaged analog display assessed P-QRS-T wave form, baseline placement and noise. Isolated individual leads judged unacceptable on initial editing were interpolated from surrounding lead site values. If >20 isolated or several clustered leads were judged unacceptable, the map was discarded from further analysis.

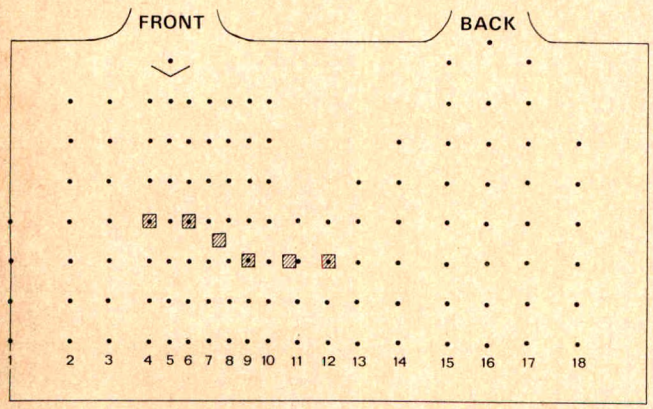

FIGURE 1. Electrode sites on the torso. The electrodes were mounted 5 cm apart, with the fourth electrode from the bottom of each strip positioned at the horizontal level of the fourth intercostal space, parasternally. The columns were placed vertically according to previously described anatomic landmarks.[5] Briefly, column 5 was placed over the sternum and column 16 over the spine. The standard V_1 to V_6 chest leads are illustrated (for reference purposes) by small **squares.**

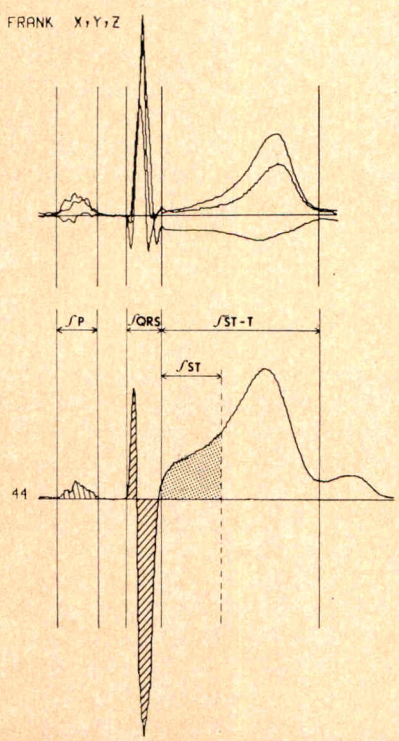

FIGURE 2. Top panel, the superimposed Frank X, Y and Z leads of a normal subject. **Vertical lines,** computer-identified time instants utilized for the various ECG time-integral measurements at each lead site. **Bottom panel,** the signal from a precordial lead of the same subject. P-wave, QRS and ST-segment time integrals are outlined by the **diagonal lines and stippling.** See text (Data Processing) for details.

Analysis of BSPM data was performed by previously described techniques.[5,10] For the purpose of this study, we focused on time-integral values of the P wave, QRS and ST segment, calculated for the averaged complexes at each torso lead site with use of time instants identified from simultaneously constructed Frank X, Y and Z leads (Fig. 2). The P-wave integral represented the algebraic sum of all potentials between the time instants of P onset and P offset multiplied by the sampling interval (that is, the net area under the P wave). The QRS integral was similarly calculated from QRS onset to QRS offset, and the ST-segment integral from QRS offset to the end of the three-eighths portion of the ST-T segment. The time-integral values were expressed as μV·s.

The data were displayed as isointegral contour maps. In this display mode, each rectangular area represents the torso surface with both vertical edges being the right midaxillary line; the left and right sides of the rectangle represent the front and back of the torso, respectively. Each contour line connects points of equal time-integral value. In individual and group-mean maps, the near-zero zone lies between areas of positive (solid contour lines) and negative (interrupted lines) time-integral values. There is a logarithmic progression of the isointegral lines away from this near-zero zone toward the numerically identified maximal and minimal values. In area-of-difference maps, constructed by subtracting the time-integral values of all lead sites in one map from the corresponding values in another, the results were also plotted in isointegral format. However, in these subtraction maps the solid lines represent torso areas where time-integral values were relatively greater in one map than in the other map; negative zones represent areas where the time-integral values of one map were relatively less than those of the other map.

Study protocol: Each subject had 8 sequential BSPM recordings. The first 2 maps were recorded during cyclic tidal respiration, 1 in the supine and 1 in the upright position. Subsequent maps were all recorded in the upright position, and with respiration arrested at end-tidal inspiration, functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV), and TLC with the addition of the Valsalva maneuver, and RV with addition of the Müller maneuver. All 8 recordings for each subject were obtained within 30 minutes, and with the same electrode application. Mean P-wave, QRS and ST-segment maps were constructed for the study group at each intervention using the group-mean values at each lead site. Mean area-of-difference maps were also constructed for P-wave, QRS and ST-segment time integrals to delineate the difference in spatial distributions between supine and upright; end-tidal inspiration and FRC, TLC and RV, TLC and Valsalva, and RV and Müller maneuver.

Intermap variability in time-integral values was also assessed by deriving a root-mean-square index of variability according to the formula[5]

$$\text{Root mean square variability} = \sqrt{\frac{\Sigma_1^N (X_{T_2} - X_{T_1})^2}{N}}$$

where N is the number of lead sites, X the time-integral values at a particular lead site and T_1 and T_2 any 2 map acquisition times.[5] In addition, P-wave, QRS and ST-segment root-mean-square variability were normalized by expressing the

mean index of variability for all interventions (compared with values in the upright position) as a percent of the mean data range of each time integral. The data range for each time integral was defined as the absolute difference between the respective P-wave, QRS and ST-segment group-mean maximal and minimal values in the upright position.[5]

Statistical analysis: Two-way analysis of variance was used to test the null hypotheses that there were no differences between index of variability values, or maximal and minimal values, for P-wave, QRS and ST-segment time integrals. If a null hypothesis was rejected, Tukey's multiple comparison test was then used to determine which values were significantly different.

Results

After stringent editing of the recorded data, 36 subjects (23 men and 13 women, aged 21 to 48 years) had sufficiently high quality recordings at all 8 states for further analysis. All results were determined from these 36 subjects.

The group-mean P-wave, QRS and ST-segment isointegral maps for each of the study interventions are displayed in Figure 3. With position change from supine to upright, there was a downward spatial shift of P-wave and QRS time-integral torso distributions, but no sig-

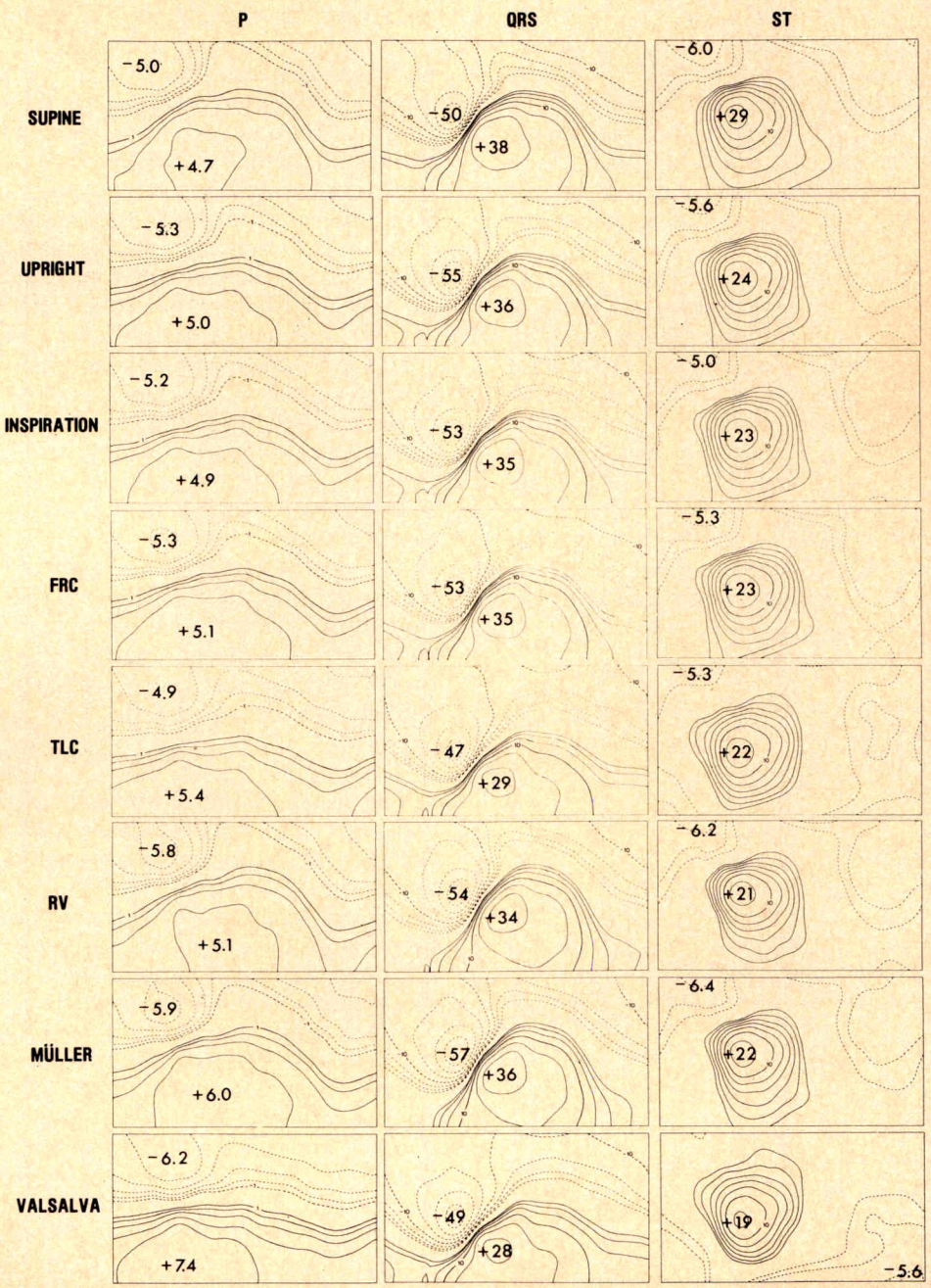

FIGURE 3. Mean P-wave, QRS and ST-segment isointegral body surface maps of 36 normal adult subjects during sequential interventions of position change and respiration. Each **rectangle** represents the torso unrolled: the **left half** reflects the anterior torso; the **right half** the back. The **contour lines** join points of equal value. The maximal and minimal values are numerically identified. FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity.

nificant change in the amplitude of P-wave or QRS maximums and minimums. ST-segment integral distributions were spatially similar in both positions. However, the ST-segment maximum significantly decreased in amplitude (29 ± 13 [± standard deviation] μV·s, supine versus 24 ± 13 μV·s, upright; $p < 0.01$). Compared with maps recorded during cyclic tidal respiration (that is, in the upright position), maps recorded with arrested respiration at end-tidal inspiration and FRC showed no apparent spatial changes in P-wave, QRS or ST-segment distributions, nor any significant changes in amplitudes of maximums and minimums. Maps recorded at TLC showed a downward torso displacement of P-wave and QRS distributions and a significant decrease in the amplitude of QRS maximum (36 ± 19 μV·s, upright versus 29 ± 17 μV·s, TLC; $p < 0.01$) and an increase in QRS minimum (−55 ± 24 μV·s, upright versus −47 ± 23 μV·s, TLC; $p < 0.01$). ST-segment spatial distributions and maximal and minimal values were unchanged at TLC, relative to values in the upright position. At RV, there was an upward spatial displacement of the P-wave and QRS distributions but no change in ST distribution or maximal and minimal values compared with those in upright maps. Maps recorded with the Valsalva maneuver showed spatial P-wave, QRS and ST-segment distributions similar to those recorded at TLC, and a similar decrease in QRS maximums, compared with distributions in the upright maps. In addition, maps recorded during the Valsalva maneuver had a significant increase in the P-wave maximum and decrease in ST-segment maximum. In an analogous fashion, maps recorded during the Müller manuever were similar in spatial distribution to maps recorded at RV, both representing an opposite, upward torso shift in P-wave and QRS distributions relative to maps recorded at TLC and with the Valsalva maneuver.

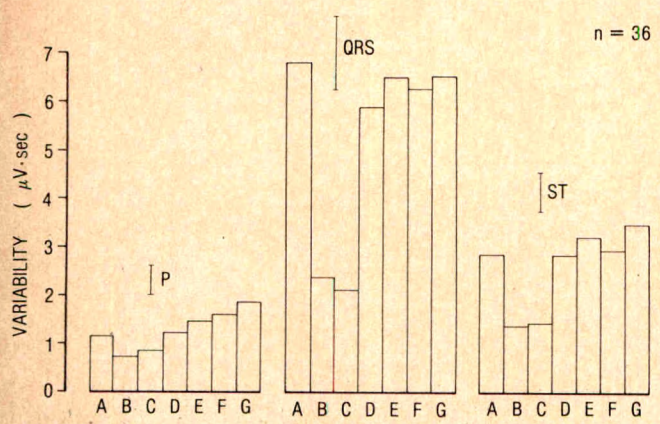

FIGURE 4. Group-mean root-mean-square variability of P-wave, QRS and ST-segment time-integral values at the body position and respiration intervention points, compared with cyclic tidal respiration in the upright position. The **letters** under each column identify the various interventions: The **bar** over each integral indicates the difference required to reach a significance level of $p < 0.05$ between any 2 interventions. A = supine; B = end-tidal inspiration; C = functional residual capacity; D = total lung capacity; E = residual volume; F = Müller maneuver; G = Valsalva maneuver.

The average root-mean-square variability between upright maps and each of the other states is illustrated in Figure 4. For each integral, maps recorded at the end points of tidal respiration (end-tidal inspiration and FRC) showed the least variability; maps recorded in the supine position and at maximal respiration points (TLC, RV, Müller and Valsalva maneuvers) showed the greatest variability.

The relative effects of position change, tidal respiration, maximal respiration, and Valsalva and Müller maneuvers on P-wave, QRS and ST-segment isointegral distributions are illustrated by the area-of-difference maps in Figure 5. As might be expected from consideration of the group-mean maps (Fig. 3) and the relative indexes of variability (Fig. 4), tidal volume respiration resulted in very small areas of difference for P-wave, QRS and ST-segment distributions. Position change and maximal respiratory volume change resulted in much greater areas of difference for all time integrals. However, the addition of the Valsalva maneuver to TLC and the addition of the Müller maneuver to RV resulted in generally small differences in any integral distribution. Intermap root-mean-square variability with these same interventions was also assessed and the results of this global assessment of map variability concurred with the spatial differences detected by the subtraction maps (Fig. 5). The least variability for all time integrals occurred with change in tidal volume. For all integrals, maps recorded at the extremes of respiratory volume were associated with the greatest variability ($p < 0.01$ versus tidal volume). For QRS and ST-segment time integrals, position change was also associated with a comparatively large map variability ($p < 0.01$ versus tidal volume).

The normalized root-mean-square variability data for the series of interventions showed that the P-wave time integral showed relatively greater variability than either the ST-segment or QRS integrals ($p < 0.01$); and the ST-segment variability was significantly greater ($p < 0.01$) than that of the QRS.

Discussion

The results of this study suggest that resting tidal volume respiration has relatively little effect on body surface ECG patterns. In contrast, change in posture from the supine to the upright position and large changes in respiratory volume may be associated with substantial changes in body surface ECG distributions. Although the P-wave integral showed the least absolute root-mean-square variability over the series of interventions tested in this study, it exhibited the greatest normalized or relative variation; the QRS integral, on the other hand, demonstrated the greatest absolute and the least relative variability. The relative constancy of the QRS wave form is consistent with results from other studies assessing temporal and exercise-associated P-QRS-T variability in normal subjects.[5,12]

Previous investigators, using both extensive[11] and limited[13–18] electrode arrays, have also described ECG changes associated with posture change and respiration. Our findings are in general agreement with those of the earlier studies, including the conclusion of Shapiro et

al[16] that postural ECG changes are greater than those that result from day-to-day variability of electrode locations. Our data suggest that this is also true for changes associated with maximal respiration.[5] The changes we found between maps recorded at the arrested end points of tidal respiration were, on the other hand, relatively small in magnitude and similar to the temporal variability previously described to occur during cyclic respiration with the same application of electrodes.[5] Similarly, our data are in agreement with those of Flaherty et al,[11] who described an inspiration-associated inferior torso shift and decrease of anterior QRS potentials in children. However, with our techniques we demonstrated that the inferior torso shift and decrease of QRS time-integral values with inspiration were marked only on deep inspiration.

Many explanations for the changes in the ECG appearances associated with position change and respiration have been proposed, including positional change of the heart in relation to the recording electrodes, alterations of vagal and sympathetic tone, differences of ventricular volume, variations in coronary artery flow and variations in electrical resistivity with changing lung volumes.[17] This study was not designed to resolve the underlying causes of ECG differences secondary to position change and respiration, but the results do suggest that the shifts in ECG distributions consequent to change from the supine to the upright posture and with maximal respiratory volume are associated with a similar physiologic change, most probably a common downward shift of the cardiac electrical source in relation to the recording torso electrodes. Although deep inspiration resulted in similar spatial shifts of P-wave and QRS distributions, there was a contrasting effect on the values of the P-wave and QRS maximums (P-wave maximum was unchanged and the QRS maximum decreased). These findings suggest that although large lung volumes may have a significant insulating effect on cardiac potentials during ventricular depolarization, they do not appear to affect all cardiac potentials equally. Because, in the absence of any other factor, one would reasonably expect a common insulating effect on all ECG potentials with increased lung volumes, these findings suggest that other factors are operative. These presumed other factors associated with deep inspiration, for example, increased intracardiac blood volume or change in sympathetic tone, may have contrasting effects to the increased electrical resistivity produced

FIGURE 5. Mean P-wave, QRS and ST-segment subtraction maps spatially locating the areas of difference for each time integral between sequential maps recorded at the following: supine and upright positions; end points of tidal (inspiration − FRC) and maximal (TLC − RV) respiration; and end points of maximal respiration with Valsalva (TLC − Valsalva) and Müller (RV − Müller) maneuvers. **Solid lines,** torso areas where maps recorded at the time of the previous intervention had greater integral value than maps recorded at the succeeding intervention; **interrupted lines,** areas where the previous maps had relatively less integral values compared with the succeeding state. The greatest areas of difference occurred between maps recorded at TLC and RV, that is, with maximal respiration; the least areas of difference occurred between maps recorded at the end points of tidal respiration. Blank maps indicate no differences in time-integral values greater than 1 μV·s between interventions. Abbreviations as in Figure 3.

by the increase in lung volume. Although these hypothesized, contrasting other factors may not manifest an effect on the large potentials of ventricular depolarization, they may exert a significant effect on the relatively much smaller potentials associated with atrial depolarization and ventricular repolarization.

The major implication of these findings is that ECG changes associated with other interventions, but including posture changes or respiration (for example, during exercise testing or in the course of ambulatory ECG monitoring), may be difficult to differentiate from those induced by respiration or posture change alone. Further work is required to define more fully the spectrum of body surface ECG changes in other physiologic states and in other populations (for example, patients with coronary artery disease) and to further explore the underlying electrophysiologic mechanisms of these changes.

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An Ambulatory Ventricular Function Monitor: Validation and Preliminary Clinical Results

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A device for the continuous measurement of left ventricular (LV) function was tested in a series of 34 subjects. The instrument consisted of 2 arrays of radiation sensitive cadmium telluride detectors held in place over the region of the left ventricle and lung by a vest-like garment (hence the name VEST). The VEST electronic instrumentation included analog-to-digital converters, a battery pack, microprocessor and gating device, which were worn in a back pack. Data generated by the VEST, including the digitized average electrocardiogram, RR interval, counts/13 ms in each radiation detector, and time since commencement of data recording, were recorded on a cassette tape recorder every 2 minutes for subsequent analysis. At the conclusion of conventional multigated blood pool imaging, the VEST was positioned and worn by the subjects while supine, standing in place and walking. The correlation of ejection fraction calculated independently from the VEST and scintillation camera data was >0.95. The inter-record reproducibility of the ejection fraction measured by the VEST in sedentary subjects was <3%.

(Am J Cardiol 1983;52:601–606)

Radionuclide angiography at rest and exercise is frequently used to define both basal and reserve left ventricular (LV) function in patients with a wide array of cardiac disorders.[1–5] The stress commonly used for the procedure, large-muscle dynamic exercise, may not be representative of the types of everyday stress placed on the patient.[6] While performing ordinary activities of daily living, such as eating a meal, psychologic stresses or exposure to severe temperature changes, LV function may vary over a wide range in both the healthy and diseased heart. The changes in LV function brought about by these activities may equal or exceed those during the performance of a large muscle dynamic exercise test. To measure LV function while patients carry out their usual daily activities requires a means of measuring LV function outside of the hospital environment. In 1979 a device was constructed that would permit the ambulatory measurement of LV function.[7,8]

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In this report we describe the initial results from a series of sedentary and ambulatory subjects with the prototype ambulatory LV function monitor, designed to be carried in a garment (VEST). This instrument simultaneously records the patient's average electrocardiogram, heart rate and nuclear data from the left ventricle and lungs in a form suitable for calculating LV ejection fraction and relative pulmonary blood volume.[9]

Methods

The ambulatory ventricular function monitor (VEST): The VEST consists of a pair of solid-state radiation detectors, gating apparatus, microcomputer and data recorder (Fig. 1). The instrument records the digitized electrocardiographic wave form averaged over 2 minutes, RR-interval histogram, and summed counts/13 ms from 2 radiation detectors, 1 placed over the left ventricle and 1 placed over the lungs. Commencing with the R wave, the count data from each nuclear detector is entered into a buffer memory each 13 ms. When the next R wave occurs, the process commences for the next beat into another memory. The previous cycle is then tested to determine if its length is within ±20% of the average of the previous 4-beat interval. If so, the data are considered normal and are added to those recorded previously in the average data buffer; those that are short or long are filed separately. Every 2 minutes, the information in memory is recorded on a capstan-drive pocket tape recorder for evaluation at the conclusion of data collection.

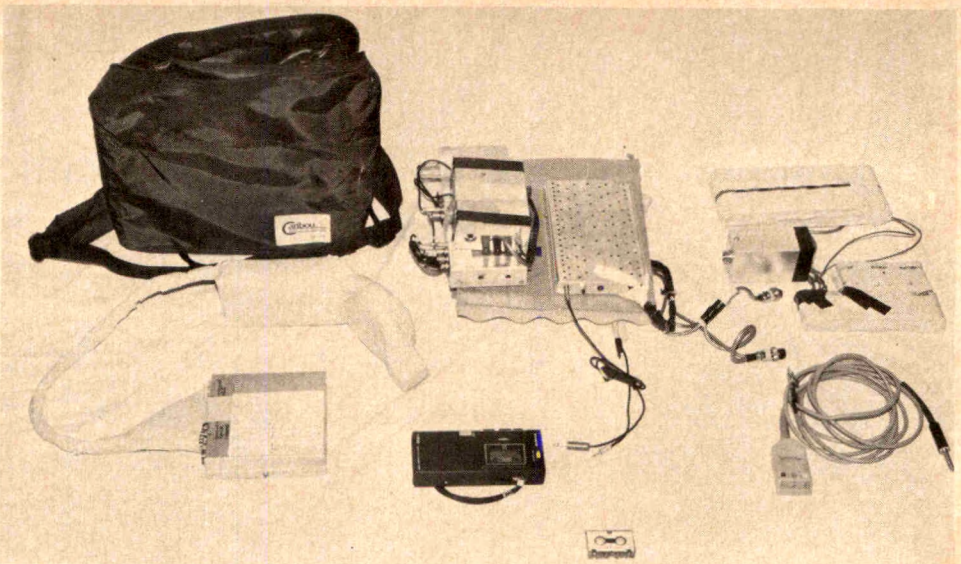
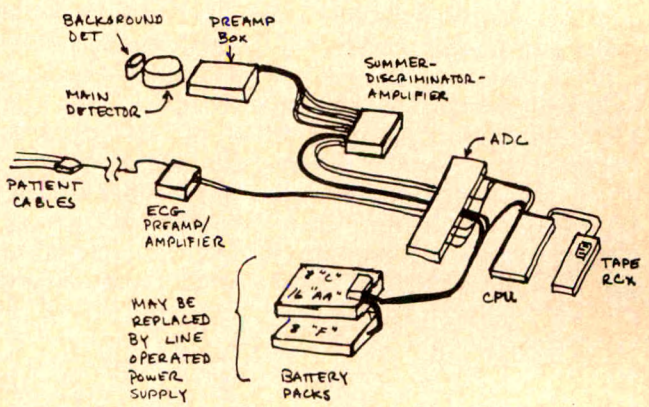


FIGURE 1. Top, VEST components in backpack. **Bottom,** exploded schematic of individual modules.

The radiation detectors consist of cadmium telluride crystals placed behind parallel-hole collimators (Fig. 2). After initial amplification, the output from the LV and lung background detectors is subject to threshold analysis and the composite signals are summed for 13 ms and recorded in the computer memory. The electrocardiographic data are digitized and stored in parallel with the nuclear data.

At the conclusion of the acquisition, the tape is read into a nuclear medicine computer and the R-R histogram, electrocardiogram and time-activity curves are calculated and displayed from each detector.* From these data the average heart rate, number of aberrant beats, LV ejection fraction and relative pulmonary blood volume are calculated for each time interval.

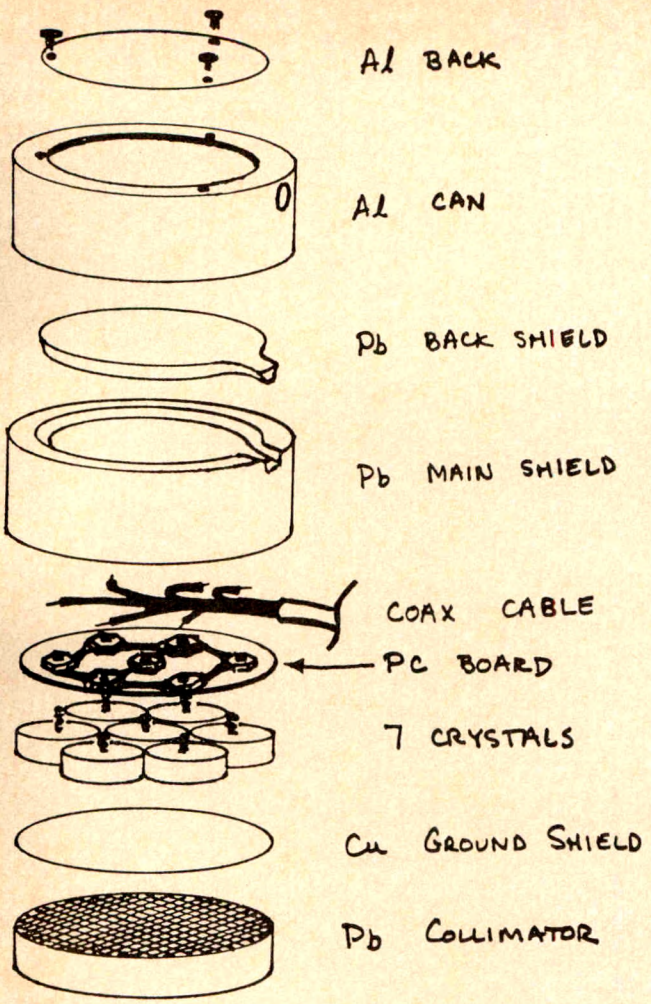
Patient studies: Multigated blood pool images were recorded in 26 patients (23 men and 3 women) as part of their evaluation for known heart disease. After in vivo red blood cell labeling as described by Callahan,[10] baseline multigated imaging was performed with a Technicare 420 scintillation camera equipped with an all-purpose, low-energy, parallel-hole collimator in the anterior, left anterior oblique and left posterior oblique views.[11] The data were recorded in a dedicated nuclear medicine computer system (Technicare 550) in a 16-frame (anterior and left posterior oblique) or 32-frame (left anterior oblique) 64 × 64 word mode matrix. At the conclusion of blood pool imaging, the persistence oscilloscope of the gamma camera was used to position the VEST foreground detector over the left ventricle in the 35 to 50° left anterior oblique projection that best separated right and left ventricles. The background detector was placed over a left paraventricular region that did not contain the descending aorta or spleen. The position of the VEST detectors was confirmed by acquiring a 30-second static image with the gamma camera (Fig. 3). The VEST detectors were affixed to the patient's chest with a sling and an elastic binder (Fig. 4). The batteries, microprocessor and tape recorder were carried in a small backpack. The weight of the entire apparatus is 5.5 kg.



To compare the VEST ejection fraction to that recorded with the scintillation camera, an initial set of VEST data (4 to 6 minutes) were recorded with the patient supine. The gamma camera was then moved aside and the patient was brought to a standing position for 6 to 8 minutes longer. The VEST was then removed and a second set of scintillation camera images was recorded in the standing position. In 15 patients who were too ill to stand, continuous data were recorded in the supine position. The ejection fractions were then determined independently by 2 observers: 1 calculated the ejection fraction from the gamma camera data with a varying region of interest count-based method and 1 analyzed the numerical data from the VEST.

Eight additional patients wore the VEST apparatus for ≤30 minutes while performing some ordinary activities in the hospital, such as walking in the hall, using the bathroom, sitting and reading, and quiet conversation. Gamma camera confirmation of ejection fractions were obtained in these patients in the sitting position, just before initial placement of the VEST, and in the standing position at the conclusion of VEST data recording.

*Differences in main detector (FG) and background detector (BG) sensitivities were determined using a technetium-99m flood source. The ratio of FG to BG probe sensitivities was then used to correct for the lower sensitivity of the background probe. The measured correction factor of FG = 2.3 × BG was found to remain stable over time. Confirmation of this correction factor was obtained before each patient study. Background counts multiplied by the correction factor were subtracted from the data recorded by the FG detector to generate the LV function curve. No other correction factors were used to calculate LV ejection fraction from the VEST.



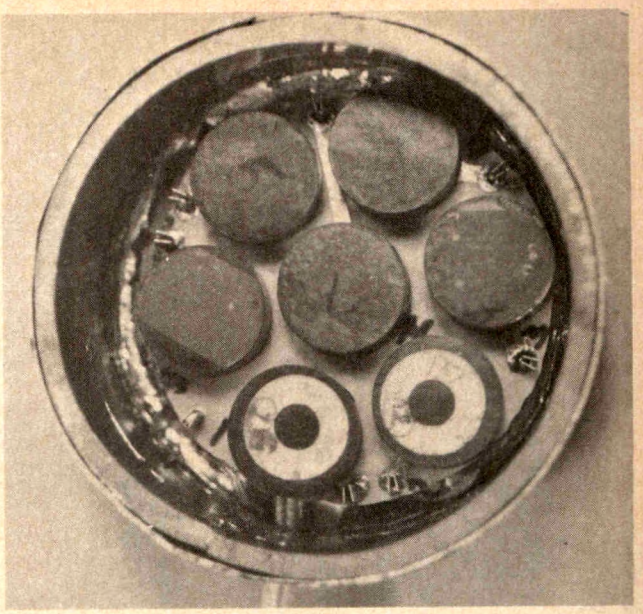


FIGURE 2. Left, main detector assembly, exploded view. **Right,** detector mosaic in housing viewed from patient side.

Ejection fractions calculated from the VEST data were compared with those calculated from the scintillation camera multigated images using a least-squares linear regression analysis.

Results

Correlation between the VEST and gamma camera–acquired LV ejection fractions are shown in Figure 4 for the supine-standing studies and in Figure 5 for ambulatory patients. For the supine/standing subjects, the LV ejection fraction correlation coefficient was 0.95 in both the supine and standing positions ($y = 1.49 + 0.98x$) (37 measurements on 26 patients, since some subjects were too ill to stand). Ejection fractions <50% (gamma camera) were observed in 16 patients. The correlation coefficient in this group was 0.92. In the sitting and ambulatory situations, the VEST and gamma camera ejection fraction correlation coefficients before and after ambulation were 0.98 ($y = 5.0 + 0.98x$) ($n = 8$). A comparison of the ejection fraction measured with the VEST on a single 2-minute record to that observed in the next 2-minute record revealed a record-to-record variation of <3%.

The results of a representative patient study recorded during the ambulatory validation phase are shown in Figure 6. The rest sitting ejection fractions determined during the first 8 minutes of the study are quite constant and closely match the LV ejection fraction obtained from the gamma camera before attachment of the VEST apparatus. During ambulation over the next 6 minutes, the ejection fraction increases slightly and after ambulation, with the patient standing, the ejection fractions from the VEST and gamma camera are similar.

Discussion

A practical nonimaging device for the repetitive measurement of LV function after equilibration of an intravascular tracer was described in 1976 by Wagner et al.[12] Initial studies with the instrument identified the requirement for precise positioning of the detector over the left ventricle to assure a correct measurement of LV ejection fraction.[13–16] Even with the positioning problems, however, investigators who have mastered the "positioning algorithm" have found excellent correspondence between gated probe measurements of

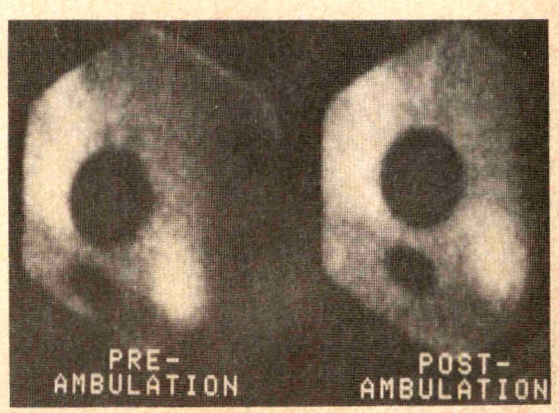


FIGURE 3. Pre- and postambulation positioning images.

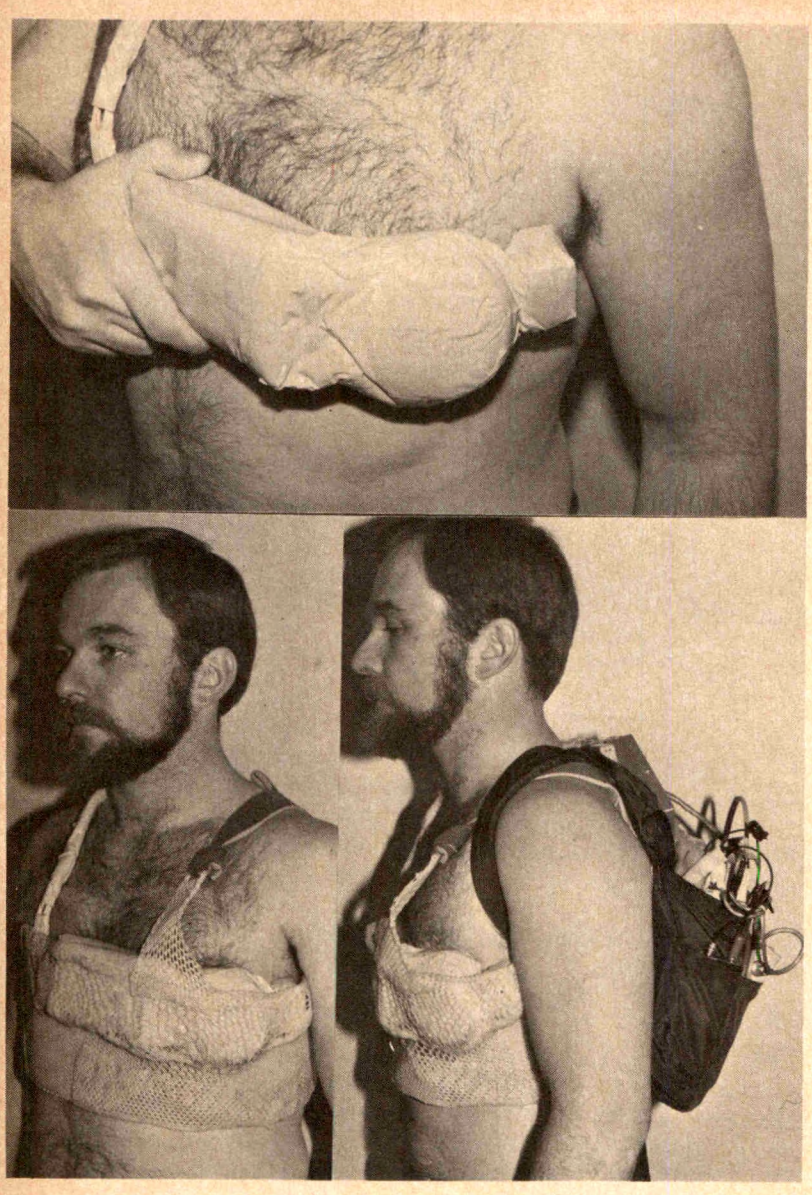


FIGURE 4. Top, detectors and preamplifier assembly on chest. **Bottom,** VEST on volunteer demonstrating thorax geometry and support device.

ejection fraction and those recorded with a gamma camera or contrast ventriculography.[13] The purpose of the VEST is to extend the ability to make continuous measurements of LV function from the bedside to an ambulatory environment. The prototype instrument digitizes, averages and records the electrocardiogram and time-activity curve data from two nuclear detectors to a cassette tape for subsequent analysis. Since this prototype was developed, state of the art electronics would now permit the simultaneous recording of additional physiologic variables, such as blood pressure and ventilatory function, in parallel with the multilead ECG and radionuclide data. These additional measurements will be particularly helpful to characterize changes in LV function during daily activities.

A critical problem with the VEST is the ability to initially place the detectors over the left ventricle and lung and to maintain this relationship during ambulatory activities. This was accomplished by placing the flat, small, radiopaque VEST detectors under direct vision using the scintillation camera persistence oscilloscope. The detectors were positioned to obscure the LV silhouette in the left anterior oblique position that best separated the left ventricle from other chambers and great vessels before fixation. Fixation of the device to the chest was accomplished with a harness and sling apparatus, similar to that used in women's foundation garments.

The correlation between ejection fraction measured with the VEST apparatus and that determined by the gamma camera in the sedentary patients suggest that technical portions of the VEST work properly. The ability to hold the detectors in place during mild physical activities was investigated in the 8 ambulatory subjects. The correlation between the VEST- and gamma camera–determined ejection fraction at the commencement and conclusion of monitoring suggest that the apparatus remained appropriately positioned with reference to the heart during these activities. Although 3 women were evaluated with the VEST with

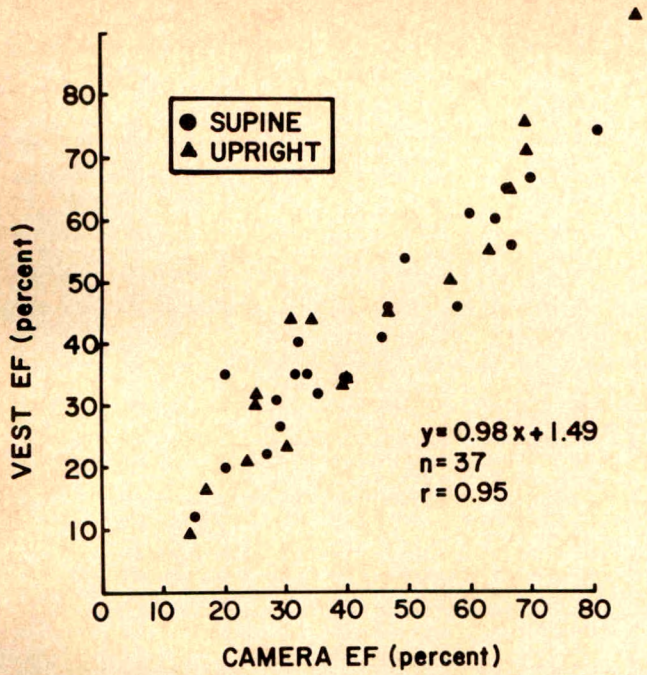


FIGURE 5. Gamma camera ejection fraction (EF) versus VEST EF (r = 0.95, n = 37, range 12–50%).

good results, fixation of the VEST detectors to persons with excessive fat or breast tissue may be difficult. However, the series of patients evaluated both supine and upright span a range of body habitus from lean to moderately corpulent.

An indication of the significance of cardiac/chest wall motion on the measured ejection fraction should be apparent when a patient changes from the supine to the standing position. The correlation of the VEST ejection fraction to that of the gamma camera under this circumstance remained good. These observations suggest that the instrument can be positioned to measure LV function and will provide valid data during the performance of moderate physical activities. The VEST data indicated no meaningful change in ejection fraction for the group of patients when changing from the supine to the upright position, probably because these patients had heart disease. This observation differs from that of Poliner et al[17] with the scintillation camera in healthy volunteers, in which a small increase in LV ejection fraction was observed from the supine to the sitting position.

The prototype VEST device[7,8] was designed to monitor electrocardiographic information and LV function for ≤24 hours. This is feasible, based on recent experience with improved red cell labeling techniques, which permit imaging of patients for gastrointestinal bleeding for >24 hours.[18] After administration of 20 mCi of technetium-99m red cells labeled with the modified in vivo method, the count rate of the main detector was high enough to permit collection of adequate data to calculate the ejection fraction in <15 seconds. Over 24 hours, the biologic loss of label from the red cells is minimal, while physical decay causes a 16-fold decrease in count rate. Therefore, a data collection interval of 240 seconds is required to calculate the ejection fraction with the same statistical reliability as would be available immediately after injection. This could be achieved either by adding data from sequential time intervals together (for 26- or 39-ms sampling throughout the cardiac cycle) or summing 3 sequential records. This endurance aspect of the instrument was not tested during this early phase of investigation.

The design criteria for the instrument were to simulate as closely as possible the qualities of a scintillation camera for determining ejection fraction. As a result, a parallel-hole collimator was selected, in contrast to the single-channel, tapered collimator used in the nuclear stethoscope device described by Wagner et al,[12] the probe device and probe simulation studies performed by Bacharach et al,[13] and the more recent studies by Hoffer et al[19] with a small cadmium telluride detector. To avoid the problems of sampling only a portion of a large dysfunctional ventricle, the foreground detector of the VEST was made large enough to sample activity from a major portion of, if not the entire, left ventricle (sensitive area >6 cm at the surface). This detector area is larger than that used by Hoffer et al[19] in their studies with a single cadmium telluride detector. These small technical changes may explain, in part, the better correlation of probe-determined ejection fraction in the present study (r = 0.95) compared with that reported by Hoffer et al (r = 0.76).

In contrast to previous studies using single probes, where pulmonary background activity was measured once, the VEST incorporates a second detector to permit continuous monitoring of blood pool activity in the lung. The additional data sought from this measurement (in addition to a background correction) is based on the studies by Nichols et al[20] and Okada et al.[9] These

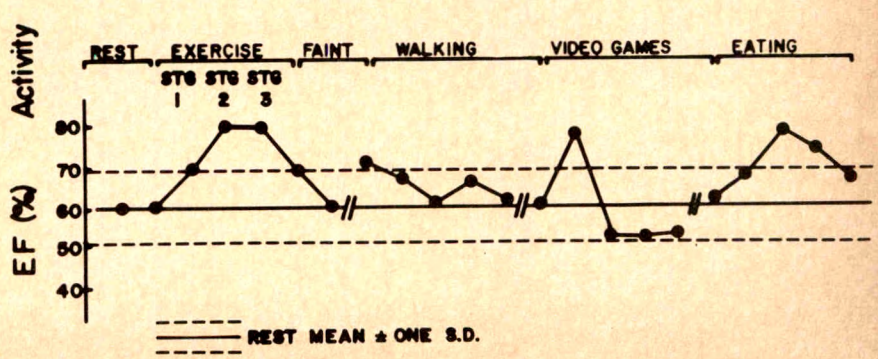


FIGURE 6. Pilot long-term monitoring study. EF = ejection fraction; S.D. = standard deviation.

investigators observed that the relative pulmonary blood volume, as measured by changes in the lung blood pool activity, is an independent and sensitive measure of alterations in LV function and, particularly, LV filling pressure.[21]

Although the anatomic and hemodynamic data obtained in the catheterization laboratory provide the basis for modern cardiac diagnosis, patients with less severe disease who are not candidates for catheterization may benefit from improved characterization of their myocardial perfusion and function available from noninvasive studies. Most of these measurements are accomplished in the laboratory, under rigorously controlled conditions. However, just as Holter ambulatory monitoring has added a new dimension to the evaluation of cardiac patients and the understanding of cardiac pathophysiology, it is likely that the ambulatory monitoring of ventricular function will also provide additional insights into the interaction of the patient's environment with his disease. Ambulatory electrographic monitoring has demonstrated an incidence of arrhythmias associated with activities of daily living that was unsuspected from monitoring limited to the laboratory.[22] For example, a patient may query whether a particular employment-related activity is safe. Although this is usually evaluated by a maximal stress test, the activity is never precisely reproduced outside the work environment. As a result, since each activity has a different impact on the heart in terms of myocardial oxygen demand or altered loading conditions, incorrect recommendations may be made, both in terms of excess conservatism and in implying safety for some excessively stressful activities. Therefore, a device like the VEST should offer important data to document the onset of cardiac decompensation.

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Hydrogen Peroxide Contrast Echocardiography

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Several agents are used as echocardiographic contrast agents, but their unreliability discourages routine clinical use. Studies from the early 1960s suggest that dilute hydrogen peroxide (H_2O_2) is a safe intravascular agent. Its use was evaluated in contrast echocardiography. To obtain dense opacification reliably, H_2O_2 (3%) was passed through a sterile 0.2 μm Millipore filter and diluted with heparinized saline solution to make a 0.1 to 0.2% solution. A drop of blood was withdrawn from an indwelling peripheral venous needle into a syringe containing 0.5 to 2.0 ml of the dilute H_2O_2 and the contents injected. Studies in dogs, normal adults and 36 patients with noncyanotic congenital and acquired cardiac disorders produced dense opacification with no complications. In vitro mixture of H_2O_2 (0.3%) with leukocyte-poor blood or plasma produced only a few microbubbles, while addition to whole blood or buffy coat produced many, suggesting a role for leukocyte peroxidase. H_2O_2 contrast echocardiography is simple, inexpensive, and reliably provides dense, sustained opacification. This study and previous studies suggest that intravenous injection of 0.2% H_2O_2 can be done safely. Great caution should be exercised in patients with severe pulmonary hypertension or large right-to-left shunts because little clinical experience with H_2O_2 is available. (Am J Cardiol 1983;52:607–609)

Contrast echocardiography is a well-recognized technique, useful in demonstrating a variety of cardiac disorders including atrial septal defect, ventricular septal defect, left superior vena cava, patent ductus arteriosus and tricuspid regurgitation.[1,2] Several contrast agents have been used in humans, including indocyanine green and aerated normal saline solution or 5% dextrose in water. Although these agents appear to be most widely used, other investigators have reported good contrast effect with the power injection of iodinated radiographic contrast material during ventriculography.[3] Surfactant-stabilized or gelatin-encapsulated microbubbles have been used in animal experiments, but appear to be too toxic for use in humans.[4,5]

Despite the ready availability of several echocardiographic contrast agents, contrast echocardiography does not appear to enjoy the widespread use one might expect. Reasons for this are not clear, but the lack of a safe, inexpensive agent that also reliably produces dense, sustained contrast effects with either M-mode or 2-dimensional echocardiography may be an important factor. Reports by Wang et al[6–8] in the People's Republic of China suggested that hydrogen peroxide (H_2O_2) might be such an ideal echocardiographic contrast agent. The present study examines this in detail.

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Methods

Preparation of materials: H_2O_2, 3%, obtained from a local cosmetics firm, was passed through a 0.2μm Millipore filter and then diluted with heparinized normal saline solution (1 unit/ml) to produce a 0.2% solution of H_2O_2 (Table I). The solution was freshly prepared for each study to ensure sterility. A drop of blood mixed in vitro with 0.2% H_2O_2 produces foam and is a simple test of the activity of the H_2O_2 being used for study.

In vitro studies: Wang et al[6] suggested that the microbubbles were formed when the H_2O_2 reacted with leukocyte peroxidase and catalase to form water and oxygen. To examine this, we mixed the dilute heparinized H_2O_2 (0.3%) with small amounts of fresh human whole blood, plasma and leukocyte-poor blood. The presence or absence of bubble formation was determined with phase contrast microscopy.

Canine studies: Initial studies in 4 mongrel dogs revealed good reproducible microbubble formation, as evidenced by dense opacification of the right side of the heart on echocardiography, so further studies were performed to investigate potential adverse effects. Five awake, unsedated mongrel dogs were used after preparation and instrumentation as described in detail by Roan et al.[9] Left ventricular, left atrial and aortic pressures were measured and an electrocardiogram was obtained. Ultrasonic crystals were used to evaluate left ventricular segmental myocardial function. Serial injections of 1, 2, 5 and 10 ml of 0.3% heparinized H_2O_2 solution, activated with autologous blood, were made through the left atrial

TABLE I Method of Preparation of Hydrogen Peroxide (H_2O_2) for Injection

Hydrogen peroxide 0.3%
↓
0.2 μm Millipore filter
↓
Dilute to 0.2% with heparinized saline (1 U/ml)
↓
0.5–2.0 ml of dilute, filtered 0.2% H_2O_2 in small syringe
↓
Withdraw a drop of blood into the syringe, mix and inject immediately in right antecubital vein with butterfly needle

catheter to allow the microbubbles full access to the cerebral and coronary circulations.

Human studies: In initial studies performed in the investigators, 1 to 5 ml of heparinized 0.3% H_2O_2 solution was injected, but this amount often provided too much contrast effect (that is, a "white-out" of the right-sided chambers and vessels for 1 to 3 minutes) so smaller quantities were then used. Two milliliters of 0.2% H_2O_2 were used in all subsequent studies. Withdrawing a drop of blood into the syringe just before injection of H_2O_2 (0.2%) produced a much better contrast effect; this technique was therefore used in most studies performed in humans. The blood "activates" the process of microbubble formation; therefore, the blood-H_2O_2 mixture should not be left in the small volume of the syringe or large bubbles will form. Intravenous injection dilutes the mixture and may prevent coalescence of the microbubbles. Because the subject was usually in a left lateral decubitus position for optimal echocardiographic viewing, all intravenous injections were made with a small butterfly needle in the right arm. Venous return from the compressed left arm often produced delayed or diminished opacification. The electrocardiogram was monitored during and after the injection. Echocardiographic imaging was performed with a commercially available phased array sector scanner (Varian V-3000 and Hewlett-Packard HP-77020AC).

Results

In vitro studies: Virtually no bubbles were seen when H_2O_2 (0.2%) was added to leukocyte-poor blood or plasma. The ability of H_2O_2 to generate microbubbles could be restored to leukocyte-poor blood by returning the buffy coat to the mixture suggesting that white blood cells were necessary for rapid microbubble formation.

Canine studies: Left atrial injection produced no detectable changes in heart rate, aortic blood pressure, left ventricular dP/dt (first derivative of ventricular pressure) or segmental wall motion after any of these injections. In addition, the dogs seemed unaware of the injections. However, deliberate injection of 2.0 ml of foam produced by mixing H_2O_2 (0.3%) and canine blood evoked the expected responses (agitation, vocalization, ventricular ectopy and depression of segmental myocardial function).

Human studies: We performed initial studies on ourselves to determine the optimal quantities of H_2O_2 to be used for the desired contrast effect. Empirical testing led to the recommendations described above. No volunteer detected any sensation or unusual feeling in the chest after the injections, although the usual cold sensation and rarely a slight sting was felt at the injection site. No change in cardiac rate or rhythm occurred.

Studies were carried out in 36 patients. A variety of cardiac disorders, including atrial septal defect, ventricular septal defect, tricuspid regurgitation, pulmonary insufficiency, pulmonary hypertension, Uhl's anomaly and congestive heart failure, were examined. An example of the contrast effect routinely achieved with this technique is shown in Figure 1. Dense opacification of right-sided structures was achieved in all patients studied, and there were no detectable ill effects. Small amounts of right-to-left shunting were produced in 4 of 6 patients with atrial septal defects and in 2 patients with ventricular septal defects by performing the Valsalva maneuver. This confirmed the presence of the septal defect previously localized by a negative contrast effect, but produced no symptoms in any of the patients. No studies were conducted in patients with large right-to-left shunts because detection of these shunts

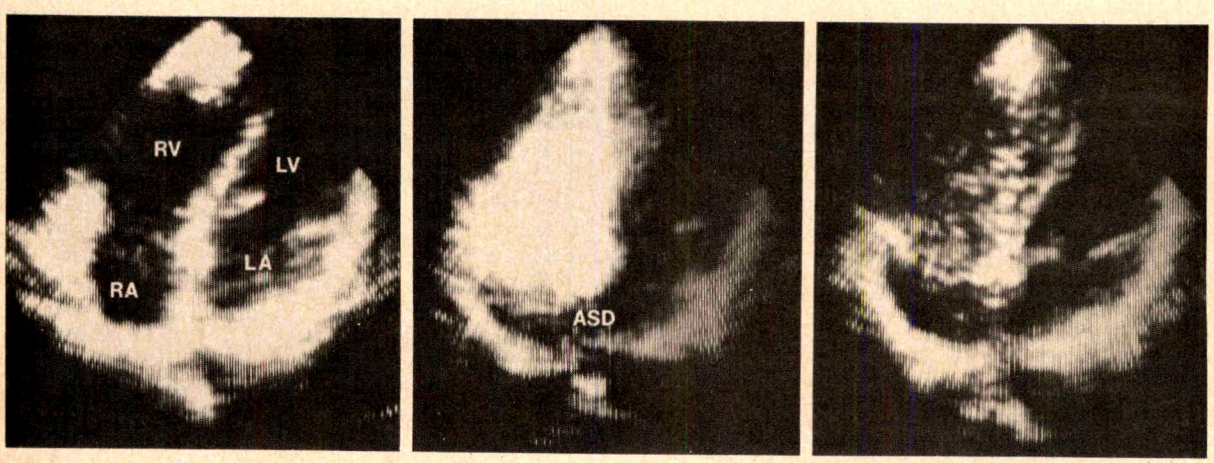

FIGURE 1. Hydrogen peroxide contrast echocardiography in a 25-year-old woman with a previously unrecognized ostium secundum atrial septal defect (ASD) and a 2.5:1 left-to-right shunt. **Left,** just before injection. **Center,** 8 seconds after injection. **Right,** 1 minute and 18 seconds after injection. Dense opacification is present except in the region of the ASD, where a negative contrast effect can be seen. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

does not require dense opacification, and aerated normal saline solution provides adequate contrast for this purpose.

Discussion

H_2O_2 is available directly from manufacturers in concentrations of 30 to 70% (wt %). These solutions are purchased by cosmetic firms and rebottled as the more dilute 3% H_2O_2 commonly sold in drug stores and other retail outlets. Deionized water is used as a diluent to prevent destabilization of the H_2O_2. The manufacturer usually adds tin and phosphate compounds for added stability and to prevent the tendency of chloride ions to pit and corrode aluminum storage vessels.[10] The American Chemical Society grade of H_2O_2 usually contains less than 20 ppm total residue on evaporation, although the highly stabilized grades contain as many as 4,000 ppm. In either case, injection of 1 to 10 ml of a 0.2% solution would not provide significant quantities of contaminants. Although the peroxide itself is bacteriostatic and fungistatic, Millipore filtering was performed before injection to eliminate particulate contamination.

Although not used for echocardiography, intravenous and intraarterial H_2O_2 injections have been used in many other clinical circumstances without apparent ill effects. These intravascular uses for dilute H_2O_2 have been described by several groups[11,12] and were reviewed by Urschel.[13] Wang noted that 6 of 11 patients with large right to left shunts developed lightheadedness, but did not note significant complications in 426 studies in 100 patients. As described previously, we used substantially lower concentrations and amounts of a purer preparation of H_2O_2, Millipore-filtered the solution and activated the microbubble formation in vitro before use and have performed over 150 injections without a single complication.

We did not introduce large amounts of oxygen microbubbles into the left side of the heart and circulation of the patients; it was not necessary clinically, and even though the oxygen should be better tolerated than air bubbles, both should probably be avoided as much as possible. Patients with large right-to-left shunts should be studied with as little contrast medium as possible to minimize the risk of the procedure. Aerated normal saline solution should be adequate for this purpose. Experience should be acquired in controlling the amount of contrast medium produced before examining patients with significant bidirectional or right-to-left shunts. Because of the unstable nature of patients with suprasystemic levels of pulmonary hypertension, any microbubble technique might produce complications and should be done with extreme caution, if at all. We did not attempt to produce myocardial opacification, although the doses used in our study were well within the nontoxic range recently reported by Gross et al[14] in a canine model.

Injection of the dilute, heparinized 0.2% H_2O_2 solution, preactivated with autologous blood, provides dense opacification of the right heart chambers and vessels. The microbubbles may be present for a few seconds to a few minutes, depending on the amount of contrast agent injected as well as venous return from the arm, the cardiac output and the presence of valvular regurgitation. Unless an intracardiac defect is present, peripheral venous injections do not produce visible left-sided microbubbles. This is consistent with other peripheral venous contrast agents, although injection from a pulmonary artery wedge position might be expected to produce a contrast effect on the left side of the heart.[15] Whether injection of massive amounts of H_2O_2 (0.2%) into the venous circulation would permit unreacted H_2O_2 to reach the arterial circulation is not known but is unlikely.

The present study was not designed to document the utility of contrast echocardiography in specific disease states, but rather to determine the safety and efficacy of a new agent, H_2O_2, for that purpose. In the small number of studies performed, H_2O_2 appears to be a safe, reliable and very effective agent. Although formal comparisons were not made with indocyanine green or specially aerated normal saline solution, the ability of H_2O_2 to produce dense, sustained contrast effects in every subject tested would appear to make it superior to other widely used agents. Dilute H_2O_2 (0.2%) is an extremely potent microbubble generator. As with any intravenous agent, care should be taken to provide sterility, correct dilution and the minimal effective dosage. As with any new agent, further studies in larger numbers of patients should be performed to confirm these findings.

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Effect of Coronary Reperfusion on Myocardial Hemorrhage and Infarct Healing

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Early coronary reperfusion for treatment of acute myocardial infarction is a promising mode of therapy but may result in hemorrhagic infarction. The effect of hemorrhage on healing of myocardium subjected to early reperfusion is unknown, but could be detrimental. To compare repair of reperfused infarcts and permanently ischemic infarcts, 2 coronary arteries were occluded in 14 anesthetized dogs, and after 4 hours, 1 artery was reperfused. Either 1 or 14 days later, samples from the center of the infarcts and from normal myocardium were analyzed for hemoglobin (milligrams per gram), creatine kinase (international units per milligram of protein), and hydroxyproline (micrograms per gram) content. In an additional 7 dogs killed at 3 days after coronary occlusion, the myocardium was studied histologically. Gross subendocardial hemorrhage was present in all reperfused infarcts at 1 day; hemoglobin content was 8 ± 1 in normal myocardium and 10 ± 2 in permanently ischemic infarcts, but was highest in reperfused infarcts at 38 ± 7 ($p < 0.025$ versus permanently ischemic infarcts). Creatine kinase content in reperfused infarcts and permanently ischemic infarcts was similarly depressed (4 ± 2 and 7 ± 1 compared with 30 ± 5 in normal myocardium, $p < 0.05$). At 3 days, polymorphonuclear leukocyte infiltration was less prominent in reperfused infarcts than in permanently ischemic infarcts. At 14 days, hydroxyproline levels were similar in reperfused infarcts (9.4 ± 2.7) and permanently ischemic infarcts (10.7 ± 1.9), and higher than in normal myocardium (3.3 ± 0.4). Thus, intramyocardial hemorrhage occurs early in reperfused infarcts, is more severe than in permanently ischemic infarcts, and is associated with an altered early granulocyte response, without affecting late collagen formation.

(Am J Cardiol 1983;52:610–614)

Reperfusion of occluded coronary arteries by thrombolytic agents or by surgery has become a promising investigative therapy for acute myocardial infarction (MI). Although several investigators have shown that early reperfusion may salvage myocardium in the subepicardial portions of the ischemic zone,[1–3] experimental and clinical reperfusion may result in morphologic differences of the necrotic myocardium compared with nonreperfused infarcts, including the presence of interstitial hemorrhage and prominent myocyte intracellular contraction bands.[4–11] How these morphologic differences affect the healing process of the resultant myocardial necrosis is largely unknown. This study examines the early and late effects of reperfusion on the healing of regions of temporarily ischemic and permanently ischemic myocardium in the same dog.

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Methods

Thirty-three mongrel dogs of either sex that weighed 14 to 27 kg were sedated with acepromazine maleate (1.0 mg/kg subcutaneously), anesthetized with sodium pentobarbital (30 mg/kg intravenously), intubated, and ventilated with a Harvard respirator. The carotid artery was cannulated to monitor arterial pressure in dogs with 1 and 14 days of coronary occlusion and the external jugular vein was cannulated to administer drugs when appropriate. A left thoracotomy was performed through the fifth intercostal space and the heart was suspended in a pericardial cradle. The mid-left anterior descending coronary artery was isolated below the first diagonal branch (approximately 4 cm from the left ostium), and the obtuse marginal branch of the left circumflex coronary artery was isolated at its origin.

Each dog was treated with a bolus of lidocaine (1.5 mg/kg intravenously), and 1 isolated coronary artery was occluded

TABLE I Hemoglobin Content (mg/g wet weight)

	Age of Infarct	
	1 Day	14 Days
Nonischemic myocardium	8 ± 1	6 ± 1
Reperfused infarct	38 ± 7*	9 ± 2†
Nonreperfused infarct	10 ± 2	10 ± 2

* $p < 0.025$ versus nonreperfused infarct.
† $p < 0.005$ versus 1 day.

TABLE II Hydroxyproline Content (μg/mg dry weight)

	Age of Infarct	
	1 Day	14 Days
Nonischemic myocardium	2.6 ± 0.3	3.3 ± 0.4
Reperfused infarct	2.2 ± 0.3	9.4 ± 2.7*
Nonreperfused infarct	2.4 ± 0.3	10.7 ± 1.9†

* $p < 0.025$ versus 1 day.
† $p < 0.005$ versus 1 day.

with a Schwartz vascular clip. At 5 minutes, a second bolus of lidocaine was administered and the other isolated coronary artery was permanently tied off with a silk suture. At 4 hours, the Schwartz clip was removed from 1 vessel to allow reperfusion. The chest was then closed and the dog was weaned off the respirator. This double-occlusion model is similar to that used by Genth et al[12] and allows a comparison of the healing process of a reperfused and a nonreperfused infarct within the same heart. By reperfusing at 4 hours and not earlier, our object was to produce equally sized reperfused and nonreperfused (permanently ischemic) infarcts within the same heart. The coronary artery used for the permanent versus the temporary occlusion was alternated from dog to dog.

At 1 day, 3 days or 14 days after occlusion, the dogs were reanesthetized, intubated and ventilated as before. After the chest was reopened, an overdose of potassium chloride was administered and the heart immediately excised and placed on ice. The right ventricle, left atrium and fatty and valve tissue were dissected away. The left ventricle was then sliced into transverse sections parallel to the atrioventricular groove.

In dogs killed at 1 or 14 days, myocardial tissue was analyzed biochemically for degree of necrosis (creatine kinase [CK]), hemorrhage (hemoglobin [Hb] concentration) and scar formation (hydroxyproline [HP] content). A fresh sample (mean ± standard deviation 0.64 ± 0.22 g) was taken from the center of the reperfused MI, the center of the nonreperfused MI and from remote normal myocardium, and placed in cold saline solution to be analyzed for Hb and CK content. The tissue samples contained 50 to 60% of the infarcted left ventricular ring. Hb concentration was analyzed spectrophotometrically as previously described[8,13,14] and expressed as milligrams per gram of wet weight of the sample. CK and cardiac protein were measured by the methods of Lowry et al[15,16] and CK was expressed as international units per milligram of protein. A 50- to 100-mg sample was taken from the center of the reperfused MI, the center of the nonreperfused MI, and from remote normal myocardium for HP content which was assayed by the method of Neuman and Logan[17] and expressed as micrograms per milligram of dry weight.

Seven animals were killed at 3 days to assess the morphologic features of early healing. From the hearts excised at 3 days, large samples were cut that encompassed both the reperfused MI and the nonreperfused MI at several levels. These samples were fixed in 10% buffered formalin, embedded in paraffin and sectioned at 6 μm. Three to 7 sections (mean 5), each stained with hematoxylin-eosin, were examined from each heart. The following histologic features of myocardial damage and repair were assessed qualitatively as absent, mild, moderate or severe: necrosis, contraction bands, hemorrhage and polymorphonuclear and mononuclear leukocytic infiltration.[18,19]

In hearts analyzed at 1, 3 and 14 days, a gross assessment of the presence and character of infarction and hemorrhage was made before fixation, and the transverse slices of each heart were placed under a clear acetate sheet in order to trace the infarcted and noninfarcted zones on clear plastic sheets. The slices were subsequently photographed. The size of each infarction was determined by planimetry and expressed as a percentage of the left ventricle.

All biochemical and planimetric data are presented as mean ± standard error of the mean, and paired t tests were used to compare infarcts within the same heart; group t tests were used to compare 1- and 14-day-old infarcts.

Results

Of the 33 dogs that entered the study, 12 were excluded: 1 died upon occlusion, 8 died during the reperfusion phase and in 3, at least 1 infarction was absent. Of the remaining 21 dogs, 7 were killed at 1 day, 7 at 3 days and 7 at 14 days. Analysis of Hb and HP content was successful in all hearts; CK measurement was unavailable in 3 dogs; histologic analysis of 1 dog that died 2 days after occlusion was included.

The biochemical data from infarcts subjected to 1 and 14 days of coronary occlusion are listed in Tables I and II. At 1 day there was approximately 4 times more Hb in the reperfused MI than in the nonreperfused MI (Table I) and HP content was low in remote normal myocardium, reperfused MI and nonreperfused MI (Table II). CK levels were similar in reperfused MI (4 ± 2 IU/mg protein) and in nonreperfused MI (7 ± 1 IU/mg protein, p = NS [not significant]), but were significantly lower than in remote normal myocardium (30 ± 5 IU/mg of protein; $p < 0.05$).

At 14 days, Hb levels were significantly lower than at 1 day in reperfused MIs (Table I), which may be due to reabsorption of or denaturation of hemoglobin within the reperfused infarcts. At this time, Hb levels were similar in reperfused and nonreperfused MI. HP levels in both infarcts were significantly higher at 14 days than at 1 day (Table II). HP content was similar at 14 days in the reperfused and nonreperfused MI and higher in reperfused MI than in remote normal myocardium. At 14 days, CK levels were significantly and similarly lower in both infarct groups (22 ± 5 IU/mg protein in reperfused MI and 16 ± 8 IU/mg protein in nonreperfused MI) compared with values in remote normal myocardium (41 ± 3 IU/mg protein, $p < 0.025$). CK levels within the infarcts tended to be higher at 14 days than at 1 day.

Upon gross analysis, hemorrhage in the nonreperfused MI at 1 day was severe, dark red and confined to the inner one half of the left ventricular wall. A rim of necrotic but nonhemorrhagic tissue often surrounded

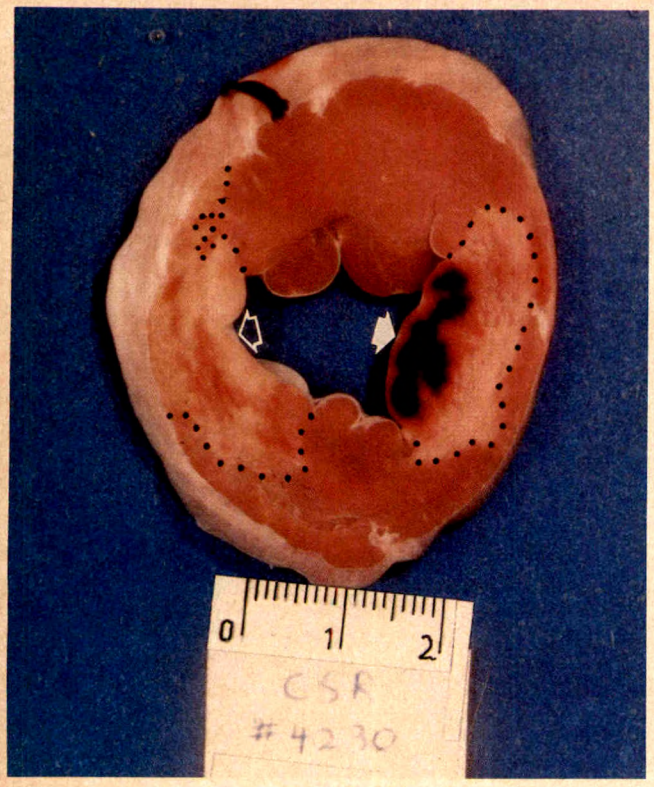

FIGURE 1. Transmural left ventricular slice from a dog that underwent 4 hours of coronary occlusion followed by 1 day of reperfusion of the circumflex coronary bed and permanent coronary occlusion of the left anterior descending coronary bed. The reperfused infarct on the right (**solid arrow**) shows an inner dark brownish hemorrhage outlined by bright red hemorrhage confined to the subendocardium, surrounded by infarcted, nonhemorrhagic, pale tissue. The permanently ischemic infarct (**open arrow**) on the left shows more diffuse and mild hemorrhage.

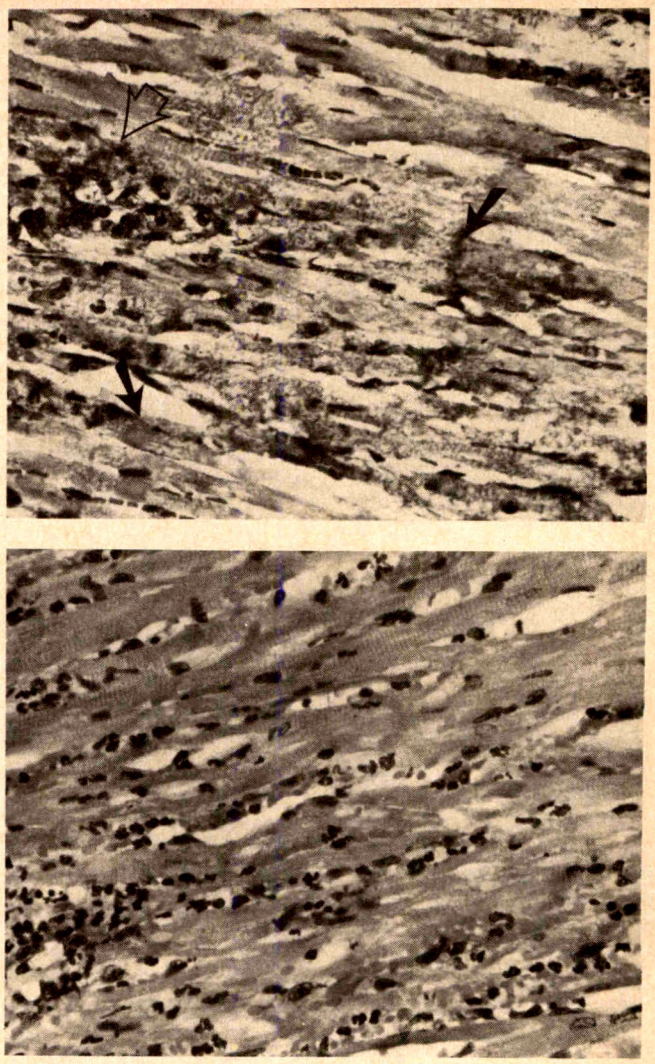

FIGURE 2. Histologic photomicrographs of infarct reperfused at 3 hours and a permanently ischemic infarct 72 hours after original ligation. **Top,** reperfused infarct demonstrating necrosis with contraction bands (**closed arrows**) and focal mononuclear cell infiltrate (**open arrow**). **Bottom,** permanently ischemic infarct with coagulation necrosis and diffuse polymorphonuclear leukocytic infiltrate. Hematoxylin-eosin stain; magnification ×375, reduced 23%.

the gross hemorrhagic region (Fig. 1). In contrast, hemorrhage in the nonreperfused MI at 1 day was mild and light pink.

The sizes of the reperfused and nonreperfused infarcts determined by gross pathologic analysis and planimetry at 1, 3 and 14 days were similar. At 1 day, the mean percentage of left ventricular area that was infarcted was 16 ± 4% for the reperfused MIs and 10 ± 2% for the nonreperfused MIs (p = NS); at 3 days, the mean percentage of left ventricular area was 12 ± 3% for the reperfused MIs and 10 ± 2% for the nonreperfused MIs (p = NS); at 14 days, the mean percentage of left ventricular area infarct was 8 ± 2% for the reperfused MIs and 9 ± 3% for the nonreperfused MIs (p = NS).

Histologic analysis of these infarcts at 3 days demonstrated that both reperfused and permanently ischemic infarcts were predominantly subendocardial, including large involvement of the papillary muscles. Although the degree of necrosis was similar in both groups, hemorrhage was absent to mild and had only small foci in permanent infarcts, while it was moderate to severe in reperfused myocardium and was localized in the subendocardium. Transverse eosinophilic contraction bands were seen at the edges of permanently ischemic infarcts but were not seen toward the center of the infarcts. They were more diffuse but similarly mild in reperfused infarcts. Histologic analysis of the dog that died at 2 days was similar to that of the dogs analyzed at 3-days.

The inflammatory response of these infarcts differed at 3 days. The polymorphonuclear leukocytic response was greater in permanently ischemic than in reperfused infarcts in the same animal. Polymorphonuclear inflammation was moderate in the permanently ischemic infarcts with multiple large foci (Fig. 2). Nevertheless, in reperfused infarcts, mild infiltration with occasional small foci was noted in nonhemorrhagic myocardium, and there was an overall tendency toward more mononuclear (histiocytic) inflammation in the reperfused infarcts. Figure 3 illustrates the different configurations of the infarcts.

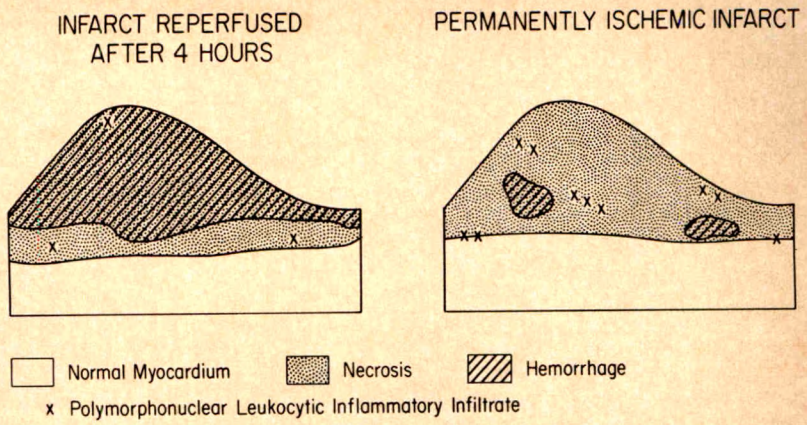

FIGURE 3. Relationship of infarct to hemorrhage and polymorphonuclear leukocytic inflammatory infiltrate at 3 days in this model.

Discussion

Deleterious effects of reperfusion hemorrhage on evolving MI have been reported by several investigators.[4–9] Extension of ischemic injury, impaired healing and functional disorders have all been implicated with intramyocardial hemorrhage. Bresnahan et al[8] suggested that hemorrhage due to coronary reperfusion leads to the extension of myocardial necrosis in the dog. Lie et al,[20] in a clinical study of patients with aortocoronary bypass and evolving MI, reported that hemorrhage not only extended the area of ischemic injury, but also impaired the histologically observed healing process. The necrotic muscle in hemorrhagic infarcts appeared dormant compared with the actively healing nonhemorrhagic infarcts.

In the present study, early hemorrhage in the reperfused infarcts was much more severe than that in the nonreperfused infarcts, as assessed grossly, histologically and by Hb content. This hemorrhage was typically located in the central and subendocardial portions of the infarction. Fishbein et al[21] and others[14] found hemorrhage only in areas of microvascular injury within the necrotic zone. The hemorrhage observed in the present study was confined to the necrotic zone and was most severe in the inner one half of the left ventricular wall, where microvascular damage would be greatest[22,23] (Fig. 1). In contrast, hemorrhage in nonreperfused infarcts at 1 day was mild, diffuse and not confined to any particular area of the ischemic zone.

Reperfusion appeared to alter the early polymorphonuclear leukocytic infiltration. At 3 days, granulocyte infiltration was less prominent in the infarction that had been reperfused, but mononuclear cell infiltration was often more prominent. It is conceivable that the granulocyte response either was suppressed throughout or had peaked at an earlier time, before biopsy. Other data,[10] however, suggest that granulocytic infiltration is not prominent at any time in the repair of this injury. The precise reason for the altered inflammatory response after reperfusion is not clear, but it may be related to the washout from the myocardium of complement-derived chemotaxins or other mediators known to be activated locally after lethal acute myocardial ischemic injury[24] or both. This phenomenon may be analogous to the rapid washout of CK demonstrated after reperfusion of myocardium with severe ischemic damage.[25] Nevertheless, there is strong evidence to suggest that the formation of granulation tissue is not dependent on the presence of neutrophils,[26] but is critically related to the action of mononuclear phagocytes.[27] The 3-day differences in the morphology of reperfused versus permanently ischemic infarcts could not be due to infarct size since the size of the infarcts was similar. HP concentrations in the center of the reperfused and nonreperfused infarcts were similar at 14 days. By gross assessment, scar size at 14 days was similar in the reperfused and nonreperfused infarct; however, the collagen content of the entire scar was not measured.

The present study assessed the effects of early reperfusion on the healing of infarction, rather than on infarct size. Previous studies,[1–3] including a recent study from this laboratory,[28] have shown that reperfusion at $\leq$3 hours of ischemia results in smaller infarcts. We did not reperfuse until 4 hours in the current study in order to create approximately equally sized reperfused and nonreperfused infarcts. This avoided the problem of interpretation that would have occurred if 1 group had smaller infarcts, which presumably might have healed more quickly than larger infarcts. Although reperfusion after coronary occlusion leads to hemorrhage into tissue that had been severely ischemic,[14] the question of how this hemorrhage may ultimately affect healing previously had not been determined.

This study suggests that intramyocardial hemorrhage induced by coronary reperfusion after 4 hours of ischemia affects the early healing process of myocardial infarction, resulting in altered neutrophil infiltration, but does not impair collagen formation. Hemorrhage was confined to the zone of necrosis.

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Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council—DHEW Publication No. (NIH)78-23, revised 1978.

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Failure of Pretreatment With Propranolol to Reduce the Zone of Myocardial Infarction After 2 Hours of Coronary Occlusion in the Primate Heart

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The present study assessed the value of pretreatment with propranolol to reduce ultimate myocardial infarct size after acute coronary artery occlusion in the primate heart. An experimental group of 8 baboons was administered a 2-mg/kg loading dose of propranolol intravenously over a 20-minute period before coronary occlusion. This regimen resulted in (1) a decrease in heart rate from 104 ± 19 to 73 ± 8 beats/min (mean ± standard deviation) ($p < 0.001$), (2) a decrease in the peak rate of rise of left ventricular pressure from 2,300 ± 340 to 1,365 ± 307 mm Hg/s ($p < 0.01$), (3) a decrease in cardiac output from 1,571 ± 249 to 1,287 ± 360 ml/min ($p < 0.001$), (4) an increase in left atrial pressure from 5.6 ± 1.9 to 9.9 ± 2.7 mm Hg ($p < 0.001$), and no significant change in mean arterial pressure. The left anterior descending coronary artery was occluded for a 2-hour period, after which perfusion was restored. A control group of 8 baboons underwent an identical procedure without propranolol therapy. At 24 hours after occlusion, microvascular dyes were injected into the coronary arteries to delineate the anatomic perfusion bed of the previously occluded coronary artery (region at risk to infarction). This allowed histologically assessed infarct size to be expressed as a percentage of the size of the perfusion bed of the occluded artery. The mean percentage of the perfusion bed infarcted in the control group was 54 ± 14% and in the treated group was 55 ± 21% (difference not significant). Hence, despite a significant decrease in heart rate and left ventricular contractility, pretreatment with propranolol did not reduce ultimate infarct size in the primate heart. The failure of propranolol therapy to result in infarct size reduction in the primate heart may be due primarily to the absence of a significant collateral circulation.

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It has been proposed that propranolol, a beta-adrenergic blocking agent, may reduce myocardial ischemia after acute coronary occlusion by reducing myocardial oxygen demand. Several investigators have observed that propranolol has a beneficial effect during acute myocardial ischemia, as indicated by a decrease in creatine phosphokinase depletion within the ischemic region[1] and a reduction in histologically determined infarct size.[2–4] However, other investigators have not shown a beneficial effect of propranolol in decreasing ischemic injury, as indicated by a failure to affect myocardial tissue creatine phosphokinase depletion[5,6] or infarct size.[7] The reasons for these conflicting results have not been clarified. However, the discrepancy may, in part, stem from the fact that there is considerable variability in infarct size, even with coronary occlusion at the same anatomic site, due to inherent variability in the size of the anatomic perfusion bed of an occluded artery.[8] Failure to control for this source of variability may lead to considerable error in the assessment of the effects of a drug on infarct salvage. Therefore, in the present study, the effect of propranolol on infarct size was examined by comparing histologic infarct size as a percentage of the anatomic perfusion bed of the occluded artery (region at risk to infarction) between control and treated baboons. This provides for a more accurate quantitative assessment of the effect of propranolol on infarct salvage. In addition, the importance of collateral

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flow to a region of ischemia in mediating the effects of propranolol was assessed by using a primate model with minimal coronary collateral circulation.[9,10]

Methods

Surgical preparation: Sixteen baboons (*Papio anubis*) that weighed 13 to 18 kg were sedated with intramuscular ketamine hydrochloride (10 mg/kg). Anesthesia was induced and maintained by intravenous injections of sodium thiopental (2 mg/kg). Baboons were intubated with a cuffed endotracheal tube and ventilated with a Harvard volume respirator maintaining an arterial pH of 7.40 ± 0.05. Arterial pressure was monitored by an 8F catheter advanced through the femoral artery. Under sterile conditions, a left thoracotomy was performed and the heart suspended in a pericardial cradle. A 3-0 mersilene snare was placed around the left anterior descending coronary artery (LAD) distal to the first diagonal branch. An electromagnetic flow catheter (Millar Instruments) was inserted into the pulmonary artery to monitor cardiac output. Left atrial pressure was monitored by way of a catheter inserted through the left atrial appendage. Left ventricular (LV) pressure and the rate of rise of LV pressure were monitored by a Millar micromanometer-tip catheter inserted through the apex of the left ventricle. Two rows of 6 unipolar atraumatic epicardial electrodes (spaced at 5-mm intervals) were sutured to the left ventricle so that they overlay the anticipated region of ischemia. The electrocardiograms were monitored with a Gould Brush Mark 260 recorder at a paper speed of 25 mm/s and a sensitivity of 1 mV/mm.

Experimental protocol: After control baseline hemodynamic values were measured, an experimental group of 8 baboons was administered a loading dose of propranolol, 2 mg/kg intravenously, in 4 equally divided doses over 20 minutes. At 10 minutes before occlusion, hemodynamic measurements were repeated after 1 mg/kg of propranolol had been administered. At 2 minutes before occlusion, after a total dose of 2 mg/kg, hemodynamic measurements were repeated and control epicardial electrocardiograms were recorded. The LAD was then occluded by tightening the snare and hemodynamic measurements and epicardial electrocardiograms were recorded at 15-minute intervals. At 2 hours after occlusion, anterograde perfusion was restored by release of the occluding snare. A lidocaine bolus (1 mg/kg) was prophylactically administered intravenously immediately before occlusion and reperfusion. The left atrial, LV and pulmonary artery catheters were removed at 3 hours after occlusion (1 hour after reperfusion) and, after closure of the chest, the baboons were returned to their cages. One baboon in the treated group died postoperatively, presumably from a ventricular arrhythmia after being returned to its cage, and was excluded from further study. At 24 hours after occlusion, immediately before killing the baboons, a bolus of heparin (5,000 U) was administered intravenously to prevent postmortem clotting of blood within the coronary arteries and thus allow for subsequent microvascular dye injections. The baboons were then killed with a rapid infusion of a saturated potassium chloride solution (arresting the hearts in diastole) and the hearts were excised. A control group of 8 baboons underwent a protocol identical to that of the experimental group except that no propranolol was administered.

Perfusion bed delineation and histologic assessment: Catheters were placed into the LAD at the site of previous occlusion, the proximal LAD, the proximal left circumflex coronary artery, and the proximal right coronary artery. These arteries were then injected simultaneously with different colored silicone rubber microvascular dyes (Microfil, Canton Biomedical Products). We have described in detail this dye injection technique,[11] which allows for accurate delineation of the perfusion bed subserved by an occluded coronary artery. After fixation of the hearts in 10% formalin for 3 days, serial cross sections of the heart were made at 3-mm intervals parallel to the minor axis of the left ventricle. A microscopic slide was made from each cross section and stained with hematoxylin-eosin. The perfusion bed of the occluded artery was readily visualized on the paraffin tissue block of the LV cross section and was marked on the corresponding histologic slide by superimposing the slide on the tissue block. Microscopic examination of each histologic slide allowed the area of infarction also to be marked on the slide. The area of the perfusion bed and the area of infarction were determined by planimetry and the areas were multiplied by the thickness of each cross section to give the respective volumes for each section. Summation of the volumes of each tissue section yielded the total volume of the perfusion bed and total volume of infarction for each heart. A mean tissue density of 1.055 for all the baboons was then used to convert the total volume of the perfusion bed and the total volume of infarction for each heart to mass.

Statistical analysis: The significance of hemodynamic and histologic changes between the control and treated baboons was examined by using Student *t* test. All values are given as mean ± standard deviation.

Results

Hemodynamics: Table I summarizes the hemodynamic results for the control and treated baboons from baseline values at 20 minutes before occlusion until 1 hour after reperfusion. At 20 minutes before occlusion, there were no significant differences between the 2 groups in any of the hemodynamic measurements. The control group of baboons had no significant changes in any of the hemodynamic measurements in the 20-minute period before occlusion. At 10 minutes before occlusion in the treated group, after a total dose of 1 mg/kg of propranolol had been administered, there were significant hemodynamic changes compared with the values 20 minutes before occlusion: (1) Heart rate decreased from 104 ± 19 to 78 ± 8 beats/min ($p < 0.001$). (2) Peak rate of increase of LV pressure decreased from 2,300 ± 340 to 1,635 ± 318 mm Hg/s ($p < 0.001$). (3) Cardiac output decreased from 1,571 ± 249 to 1,312 ± 368 ml/min ($p < 0.05$). (4) There was a small increase in left atrial pressure from 5.6 ± 1.9 to 8.3 ± 2.4 mm Hg ($p < 0.01$). There was no significant change in mean arterial pressure. At 2 minutes before occlusion, after the total dose of 2 mg/kg of propranolol had been administered, there were further significant, but smaller, changes in hemodynamic values: (1) Heart rate decreased from 78 ± 8 to 73 ± 8 beats/min ($p < 0.01$). (2) Peak rate of rise of LV pressure decreased from 1,635 ± 318 to 1,365 ± 307 mm Hg/s ($p < 0.05$). (3) Left atrial pressure increased from 8.3 ± 2.4 to 9.9 ± 2.7 mm Hg ($p < 0.001$). Mean arterial pressure and cardiac output showed no significant change.

At 2 hours after occlusion, there was a small increase in left atrial pressure from 5.1 ± 0.9 to 6.7 ± 2.3 mm Hg ($p < 0.05$) in the control group when compared with the 2-minute values before occlusion. There were no significant hemodynamic changes observed in the treated group during this same period. There were no significant hemodynamic changes in either group of baboons between 2 hours after occlusion and 1 hour after reperfusion.

TABLE I Hemodynamic Values for Control and Treated Baboons From 20 Minutes Before Occlusion to 1 Hour After Reperfusion

	20 Minutes Before Occlusion	10 Minutes Before Occlusion	2 Minutes Before Occlusion	2 Hours After Occlusion	1 Hour After Reperfusion
HR (beats/min)					
Control	116 ± 25	116 ± 25	117 ± 25	117 ± 25	123 ± 25
Treated	104 ± 19	78 ± 8*	73 ± 8†	79 ± 13	82 ± 16
Mean AP (mm Hg)					
Control	112 ± 17	113 ± 17	114 ± 14	108 ± 11	106 ± 14
Treated	111 ± 16	102 ± 19	101 ± 24	111 ± 27	112 ± 29
Peak dP/dt (mm Hg/s)					
Control	2,600 ± 617	2,570 ± 594	2,563 ± 569	2,288 ± 520	2,150 ± 444
Treated	2,300 ± 340	1,635 ± 318*	1,365 ± 307‡	1,605 ± 476	1,650 ± 437
CO (ml/min)					
Control	1,438 ± 433	1,435 ± 150	1,403 ± 416	1,284 ± 453	1,130 ± 518
Treated	1,571 ± 249	1,312 ± 368‡	1,287 ± 360	1,075 ± 275	1,162 ± 262
Mean LAP (mm Hg)					
Control	5.0 ± 1.1	5.0 ± 0.9	5.1 ± 0.9	6.7 ± 2.3‡	6.1 ± 1.1
Treated	5.6 ± 1.9	8.3 ± 2.4†	9.9 ± 2.7*	7.9 ± 2.4	9.7 ± 2.4

AP = arterial pressure; CO = cardiac output; HR = heart rate; LAP = left atrial pressure; peak dP/dt = peak value of rate of rise of left ventricular pressure.

Results are mean ± standard deviation.

* Significant change ($p < 0.001$) compared with corresponding value at preceding time interval.

† Significant change ($p < 0.01$) compared with corresponding value at preceding time interval.

‡ Significant change ($p < 0.05$) compared with corresponding value at preceding time interval.

Comparison of histologic changes between control and propranolol-treated baboons: Cross sections of the left ventricle in both control and propranolol-treated baboons showed that the perfusion bed of the occluded coronary artery was readily delineated by the microvascular dye. Hemorrhage was observed within the perfusion bed of the occluded artery in both groups. A representative cross section of the heart in a control baboon is shown in Figure 1, which shows the distinct area of the perfusion bed of the occluded coronary artery and the centrally located hemorrhage region.

Microscopic examination of hematoxylin-eosin–stained cross sections showed that the areas of infarction were completely contained within the perfusion bed of the occluded coronary artery. Infarcts characteristically consisted of a central confluent zone of infarction surrounded by a peripheral zone of small foci of patchy infarction. The infarcts showed coagulation necrosis and involved the subendocardial and midwall regions of the perfusion bed, and myocardial preservation was observed in the subepicardial and lateral regions. Some contraction band necrosis was evident in the patchy regions of infarction but not in the central zone. Hemorrhage occurred extensively within the central area of infarction and, to a lesser extent, in the patchy areas of infarction in both control and treated baboons. No hemorrhage was observed outside of the infarcted regions.

Comparison between the percentage of the perfusion bed infarcted in control and propranolol-treated baboons: Figure 2 shows the percentage of the perfusion bed infarcted for both the control (n = 8) and

FIGURE 1. Cross section of the heart from a control baboon. The previously occluded left anterior descending coronary artery was injected with yellow microvascular dye and the adjacent arteries with red dye. The perfusion bed of the previously occluded artery is readily delineated and contains a central hemorrhagic region.

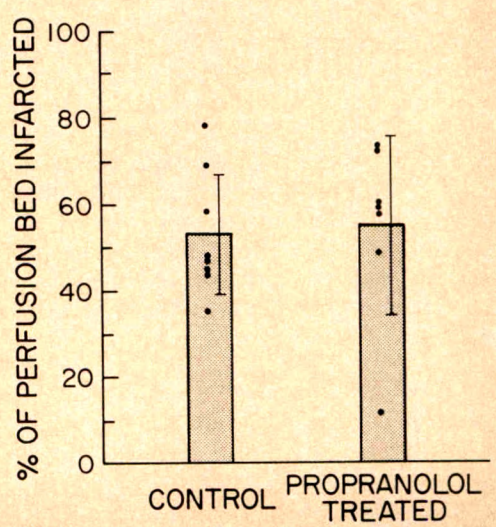

FIGURE 2. The percentage of the perfusion bed infarcted for control and propranolol-treated baboons.

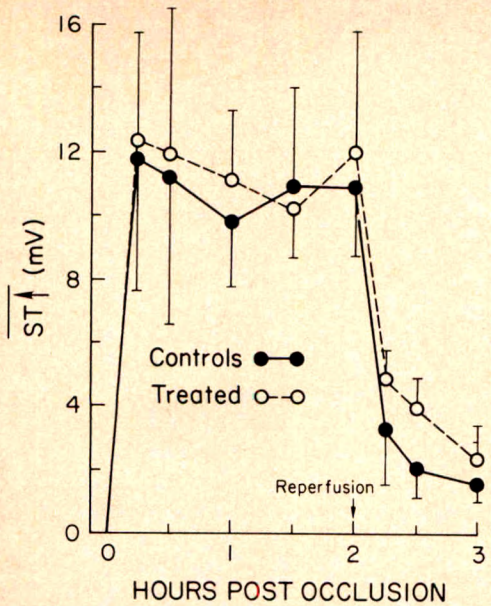

FIGURE 3. Epicardial ST-segment changes after occlusion and reperfusion in control and propranolol-treated baboons. $\overline{ST}\uparrow$ = mean ST-segment elevation.

treated (n = 7) baboons. The mean percentage of the perfusion bed infarcted in the control group was 54 ± 14 and in the treated group was 55 ± 21 (difference not significant [NS]).

A relatively consistent percentage of the perfusion bed was infarcted in both the control and treated groups, with the exception of 1 baboon in the treated group that had only 12% of the perfusion bed infarcted. The reason for this somewhat anomalous result was not evident; however, the control heart rate in this baboon was considerably slower than the others in the treated group. The control heart rate in this baboon was 68 beats/min, while the mean heart rate in the rest of the group was 109 beats/min. The heart rate after propranolol treatment was 57 beats/min in this baboon and the corresponding mean heart rate in the rest of the group was 75 beats/min.

Epicardial ST-segment changes: Figure 3 shows the epicardial ST-segment changes after occlusion and reperfusion in the control and treated baboons. Epicardial ST-segment elevation occurred immediately after occlusion and remained essentially constant during the period of occlusion in both groups, indicating ischemia of the underlying myocardium. Successful anterograde reperfusion after release of the snare was indicated by a rapid decrease in epicardial ST-segment elevation and the appearance of arterialized blood in the previously occluded artery.

Discussion

Propranolol, a beta-adrenergic blocking agent, has been widely used in experimental and clinical attempts to reduce myocardial ischemia after acute coronary artery occlusion. It has been proposed that propranolol may reduce myocardial ischemia by a reduction in myocardial oxygen consumption resulting from a decrease in heart rate and contractility.

A number of experimental studies have shown that propranolol has a beneficial effect in acute ischemia by (1) reducing epicardial ST-segment elevation within the ischemic region,[1,2,12,13] (2) reducing myocardial tissue creatine phosphokinase within the ischemic region,[1] (3) reducing histologic necrosis of the posterior papillary muscle,[4] and (4) reducing infarct size when expressed as a percentage of the left ventricle.[2,3] However, it has also been demonstrated that treatment with propranolol has failed to alter myocardial tissue creatine phosphokinase depletion after coronary occlusion[5,6] and did not result in infarct size reduction.[7] No obvious methodologic differences have been elucidated to explain these conflicting results with regard to the beneficial effect of propranolol in acute myocardial ischemia. It has been suggested that higher doses of propranolol are responsible for the failure to observe beneficial effects in ischemic injury; however, the "high dose" of propranolol used in the study of Peter et al,[5] in which a beneficial effect was not observed, was the same dosage used in several studies that demonstrated a reduction in infarct size with propranolol.[4,13] It may well be the case that propranolol, by virtue of its effects in reducing oxygen consumption, temporarily reduces the degree of myocardial ischemia; however, this does not necessarily mean an ultimate reduction in infarct size will result and may represent only a delay in the natural progression of necrosis within the ischemic region. The results of the present study, which used an accurate quantitative histologic technique of measuring infarct salvage, clearly demonstrated no decrease in long-term infarct size.

Clinical implications: Human myocardial infarction usually occurs in patients with long-standing coronary atherosclerosis who often have multiple-vessel involvement and some degree of collateralization. The impact of coronary occlusion may therefore be greatly modified by the presence of adjacent vascular lesions and by the collateral channels. Hence, the results of the present study cannot be directly extrapolated to the human situation, except perhaps for the case when acute thrombosis or embolization occurs in a single vessel in a patient with normal coronary arteries. In addition, propranolol may exert part of its action by modifying vagal or sympathetic responses, which are common in human myocardial infarction but which may be altered in the anesthetized animal. In man, the ability of propranolol, when administered within the first few hours of acute myocardial infarction, to reduce infarct size is not known, although clinical studies have suggested that propranolol may be effective in reducing myocardial ischemia during acute myocardial infarction.[14,15] Gold et al[14] demonstrated that the effects of intravenous propranolol to significantly reduce ST-segment elevation and relieve chest pain were more pronounced in patients with angiographically demonstrable blood flow to the ischemic myocardium. The reduction in ST-segment elevation with propranolol appeared to be related to the presence of collateral vessels or a subtotal occlusion of the artery. These

findings are consistent with the results of the present study, in which the failure of propranolol to reduce infarct size in the baboon may have been due to the absence of a well-established collateral circulation. In addition, we found no alteration in ST-segment elevation during the 2-hour period of occlusion when comparing control and treated baboons. Hence, propranolol may only be effective in salvaging acutely ischemic myocardium if there is significant blood flow to the ischemic region.

Effects of propranolol on the oxygen supply/demand ratio: The baboon heart differs markedly from the dog heart in the degree of collateral channels available to a region of myocardial ischemia. The dog is known to have extensive subepicardial collateral channels,[16] in contrast to minimal collateralization in the baboon.[9,10] In some studies in the dog, propranolol has been shown to improve myocardial perfusion in the ischemic region.[17,18] Hence, the failure of propranolol to reduce infarct size in the present study may at least in part be attributed to an inability to significantly increase the collateral blood flow. Peter et al,[5] who reported no effect of propranolol on infarct size, could not show an improvement in myocardial blood flow within the ischemic region in their study. Becker et al[19] showed that propranolol did not increase flow to the ischemic myocardium, but did improve the endocardial-to-epicardial flow ratio. Other investigators have found that propranolol, while reducing ST-segment elevation, actually decreased myocardial blood flow to the ischemic region.[20,21] Hence the importance of propranolol in reducing infarct size or increasing collateral flow to a region of ischemia remains unclear.

In the baboon, after coronary occlusion, there is a transmural region of severe ischemia[10] that results in the absence of contraction within this ischemic segment.[9] Even though propranolol may reduce myocardial oxygen requirements in the nonischemic regions, there will be an effect on the oxygen requirements in the noncontracting ischemic segment. In contrast in the dog, because of inherent collateral blood supply, ischemia is not as severe and some tension development can occur in the ischemic region.[12] Propranolol decreases heart work and further decreases tension development in the ischemic region;[12] this may result in a reduction in infarct size by reducing myocardial oxygen requirements.

The effect of propranolol on infarct size in this study may have been in part modified by the administration of anesthetic agents. In unanesthetized dogs, propranolol may increase collateral flow to a region of ischemia,[18] an event not observed in anesthetized dogs.[5,20] However, in baboons, because of the presence of minimal collaterals, an effect on collateral flow is less likely to be an important factor. Theroux et al[22] showed a substantial increase in heart rate in the unanesthetized dog early after occlusion of the LAD, which did not occur in the anesthetized open-chested dog.[23] The effects of propranolol in decreasing heart rate are much greater in the anesthetized animal;[18] if a significant reduction in heart rate is an important factor in decreasing infarct size, it could be argued that a beneficial response may, in fact, be more likely to be observed in the anesthetized animal.

Effects of propranolol on reperfusion hemorrhage: Propranolol has been reported to decrease microvascular injury in acute myocardial ischemia in dogs.[13,24] However, this does not appear to be a primary factor in the preservation of ischemic myocardium. As pointed out by Kloner et al,[25] ultrastructural evidence of microvascular cell necrosis lags behind ultrastructural evidence of myocardial cell necrosis, suggesting that microvascular damage is not a primary cause of myocardial cell damage. Therefore, even if propranolol exerted a protective effect on the microvasculature within the ischemic region, this would not be expected to necessarily result in a reduction in infarct size. Furthermore, in the present study, there was no difference in the degree of hemorrhage within the infarct between control and treated baboons. This observation in the baboon heart is at variance with previous reports in the dog that propranolol exerts a protective effect on the microvasculature within the ischemic region.

Dosage of propranolol and hemodynamic alterations: The moderate dose of 2 mg/kg of propranolol used in this study resulted in a significant decrease in heart rate and LV contractility, with no significant change in mean arterial pressure. There was a small but significant increase in left atrial pressure, but it remained well within normal limits. These results are comparable to those found in dog studies in which identical doses were used.[1,24] Even large doses of 5 mg/kg have been well tolerated in the dog.[4,5] Most of the significant hemodynamic changes in the present study occurred after 1 mg/kg of propranolol had been administered; the addition of a further 1 mg/kg had a relatively small effect. Hence, it appears that in the baboon model, in order to produce significant hemodynamic changes, only 1 mg/kg need be administered; however, because of the relatively small effect of the second 1 mg/kg, it is unlikely this had any deleterious effect.

In conclusion, treatment with propranolol before coronary occlusion in the baboon resulted in a significant reduction in heart rate and contractility, but did not result in a reduction in the percentage of the perfusion bed of the occluded artery that underwent ultimate infarction. The absence of a well-established coronary collateral circulation in the baboon may account for the contrasting reports by some investigators on the effect of propranolol on infarct size in the dog, in which a prominent collateral circulation is usually present. Clinically, a beneficial response to propranolol may depend on the presence of significant collateral channels or subtotal occlusion of the involved artery.

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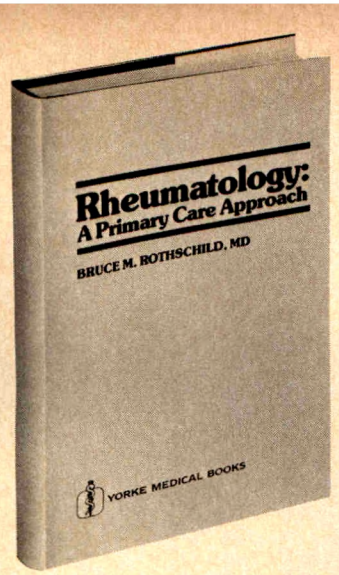

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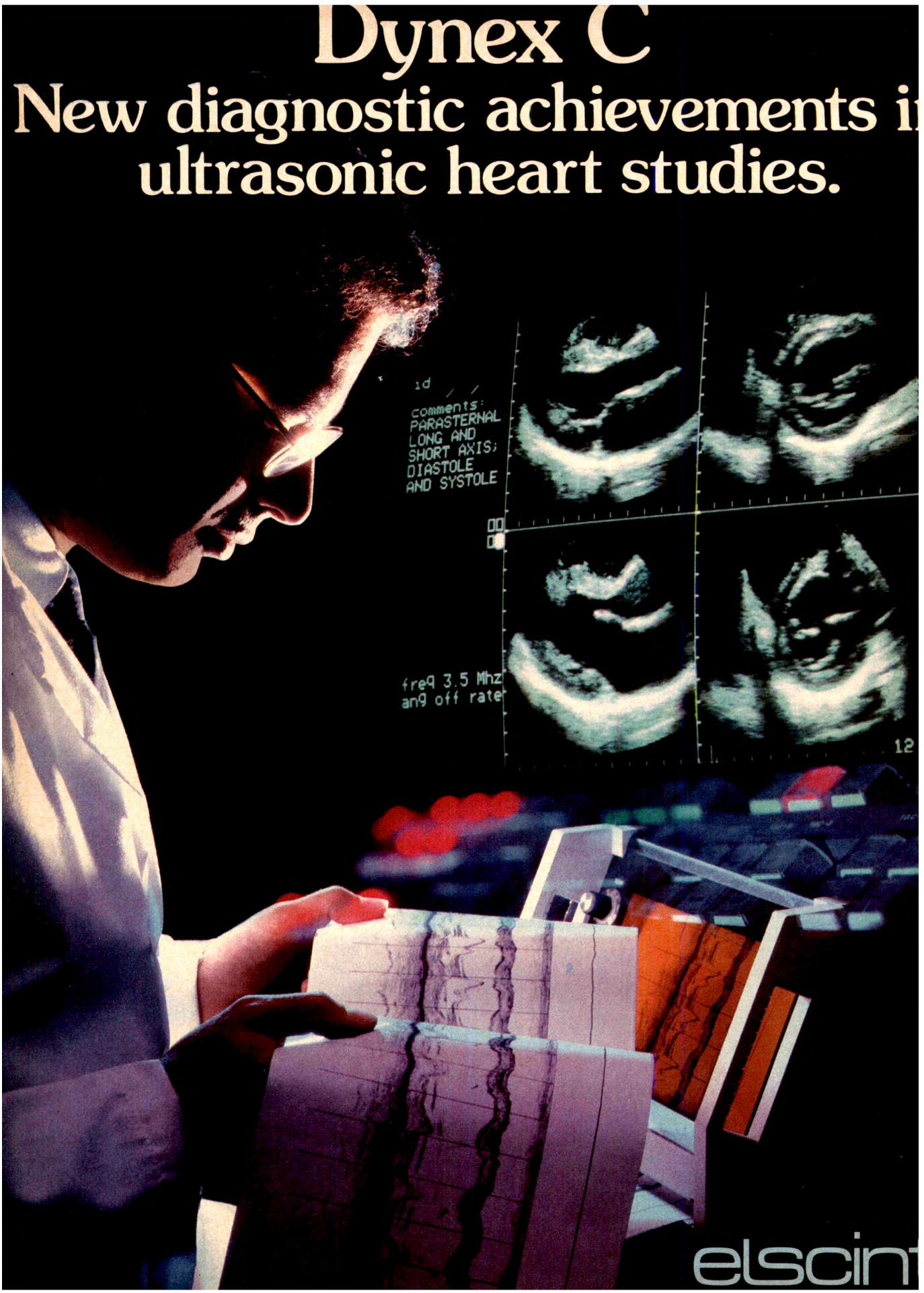

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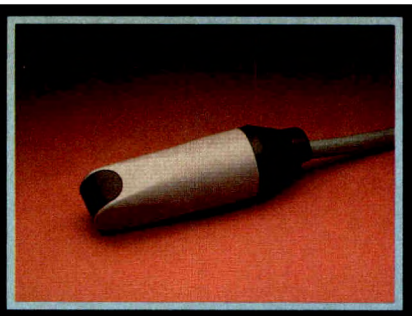

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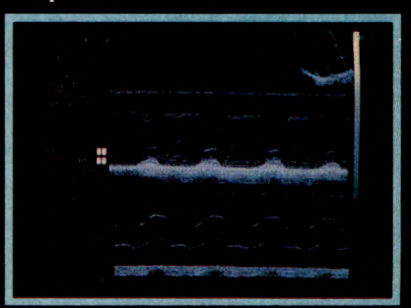

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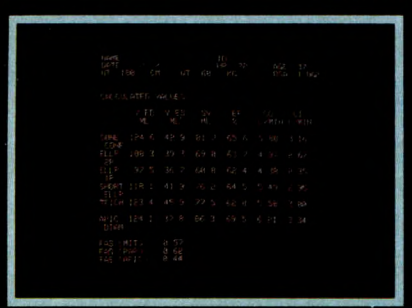

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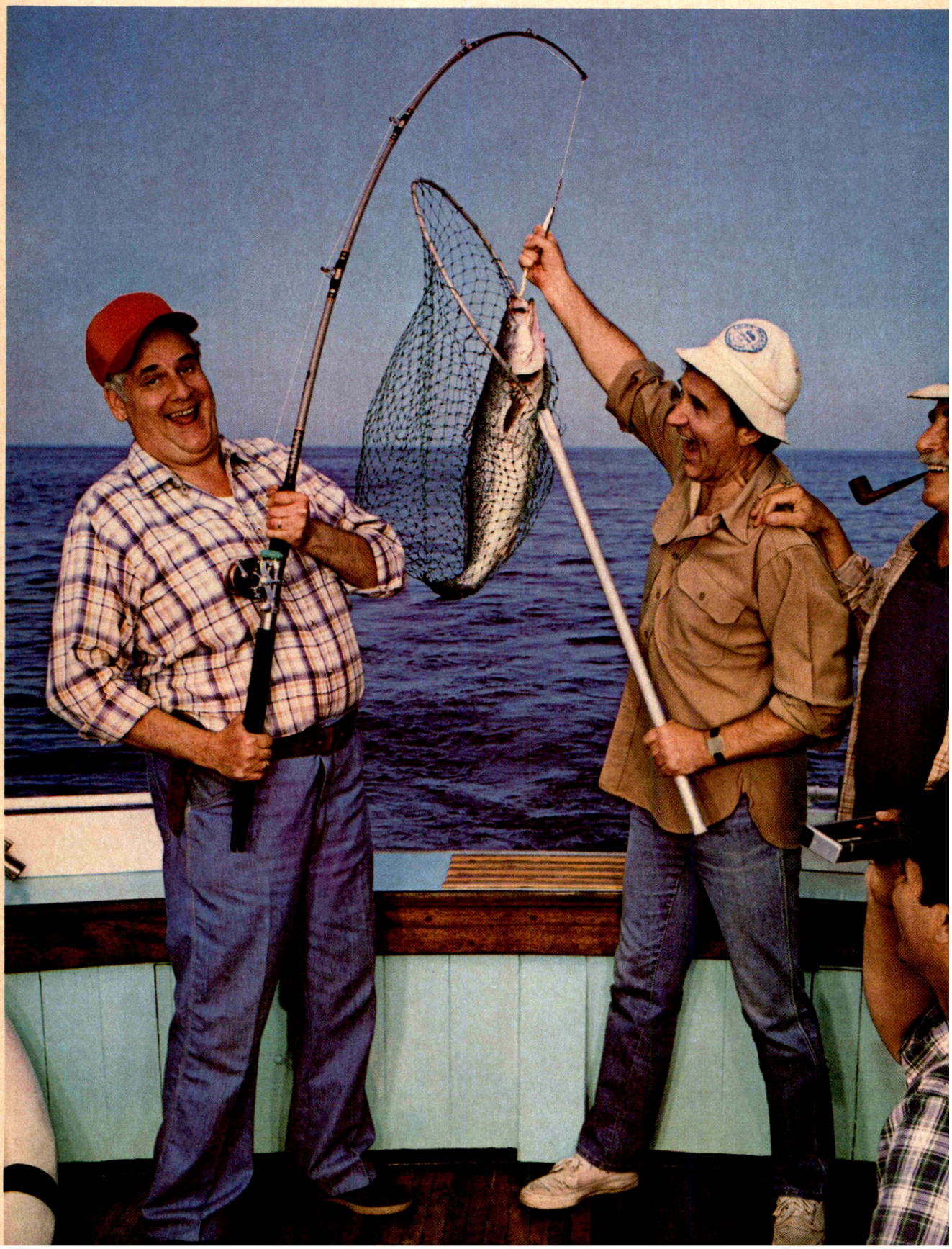

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068

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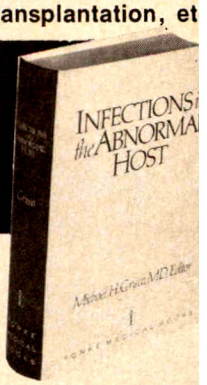

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Dose-Dependent Electrophysiologic Effects of Amiodarone in the Immature Canine Heart

ARTHUR S. PICKOFF, MD, SHARANJEET SINGH, MD, CELIA J. FLINN, MD, EDDA TORRES, MD, ALAN M. EZRIN, PhD, and HENRY GELBAND, MD,
With the technical assistance of JUDITH KASSNER *and* CARLOS A. FLORES

The electrophysiologic effects of incremental doses of intravenous amiodarone were studied in the intact neonatal canine heart and were compared with the responses observed in the adult. Seven neonatal puppies aged 5 to 14 days, and 6 adult dogs were studied. Assessment of sinus and atrioventricular (AV) nodal function and atrial and ventricular refractory periods was performed using standard His bundle recording techniques and programmed extrastimulation before and after doses of 2.5, 5 and 10 mg/kg of intravenous amiodarone. Amiodarone depressed sinus node cycle length, sinus node recovery time and AV nodal conduction in both groups. Atrial and ventricular refractory periods were also prolonged in a dose-dependent fashion in both the neonatal and adult dogs. Although similar responses to amiodarone were observed in both groups, the immature dogs were more sensitive to amiodarone in prolongation of atrial refractory periods and depression of sinus node recovery time. The neonatal group, however, demonstrated more resistance to amiodarone-induced depression of AV nodal conduction. Thus, intravenous amiodarone produces dose-dependent electrophysiologic changes in the neonate similar to those in the adult, although the significant differences in drug sensitivity may be clinically important.

(Am J Cardiol 1983;52:621–625)

Amiodarone has been proved effective in a wide variety of atrial and ventricular arrhythmias in adults.[1–5] In children, this benzofuran derivative has been reported to be well tolerated and also very effective in treating cardiac arrhythmias.[6] Recent reports have suggested that in children, amiodarone may be particularly useful in treating atrial flutter[7] and primary ventricular arrhythmias.[8] However, the electrophysiologic effects of amiodarone in the immature heart have not been defined. Information available concerning the electrophysiologic effects of intravenous amiodarone has been from studies performed in the adult. In these studies, intravenous amiodarone has been shown to prolong atrioventricular (AV) nodal conduction time (that is, prolonged AH interval), although the effects on sinus node recovery time and atrial and ventricular refractory periods have been variable.[9–13] The objective of this study is to define the electrophysiologic responses of the immature mammalian heart to incremental intravenous doses of amiodarone. These responses are compared with those observed in a group of mature animals to define developmentally determined differences in the response to amiodarone of the neonatal myocardium and specialized conduction system.

From the Division of Pediatric Cardiology, Department of Pediatrics, University of Miami School of Medicine, Miami, Florida. This study was supported in part by Clinical Investigator Award HL00881, and Research Training Grant HL07436 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland, and by a grant from the American Heart Association of Greater Miami. Manuscript received March 14, 1983; revised manuscript received May 9, 1983, accepted May 10, 1983.

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Methods

Two groups of dogs were studied: Group I included 7 neonates, aged 5 to 14 days, and Group II included 6 adults. All subjects were anesthetized with pentobarbital, 20 to 30 mg/kg, either intravenously (Group II) or intraperitoneally (Group I). All subjects underwent endotrachial intubation and were placed on an artificial ventilator with a tidal volume of 7 to 15 ml/kg.

Surface electrocardiographic lead II and right femoral artery blood pressure were monitored. Through a femoral transvenous cutdown, a No. 5 Elecath quadripolar electrical catheter (or No. 4 tripolar catheter in the neonates) was positioned under fluoroscopic visual guidance to the high right atrium to record the atrial electrogram and pacing. Through a left femoral approach in Group II or an external jugular vein approach in Group I, No. 5 tetrapolar and No. 4 tripolar electrophysiologic catheters, respectively, were advanced to the right ventricle apex. The His bundle electrogram was recorded by introducing a No. 4 tripolar catheter into the right carotid artery and advancing the catheter to the right coronary cusp of the aorta. All intracardiac electrograms were amplified at a filter setting of 40 to 500 Hz (Electronics for Medicine DR-6) and recorded simultaneously with the surface electrocardiogram and femoral artery blood pressure on direct-writing paper (Kodak linagraph paper 2201, Eastman Kodak Company) at a paper speed of 100 mm/s.

TABLE I Electrophysiologic Data

	Neonate				Adult			
		Amiodarone Dose (mg/kg)				Amiodarone Dose (mg/kg)		
	C	2.5	5	10	C	2.5	5	10
PA	10 ± 3	12 ± 2	13 ± 2	12 ± 1	17 ± 2	19 ± 3	20 ± 3	19 ± 4
AH	47 ± 5	51 ± 4	53 ± 4	53 ± 4*	52 ± 4	64 ± 4	65 ± 6	72 ± 5†
HV	13 ± 3	15 ± 1	16 ± 1	16 ± 1	32 ± 3	31 ± 2	31 ± 3	32 ± 3
Cycle length	274 ± 7	324 ± 16	347 ± 20	410 ± 33†	397 ± 31	478 ± 27	529 ± 36	597 ± 40†
%SNRT	121 ± 3	126 ± 5	128 ± 4*	127 ± 3	132 ± 6	127 ± 3	126 ± 5	125 ± 4
CSNRT	60 ± 8	83 ± 16	102 ± 12*	112 ± 11†	124 ± 20	122 ± 12	131 ± 19	150 ± 21
Wenckebach	152 ± 7	173 ± 8*	191 ± 10*	194 ± 7†	193 ± 13	240 ± 15	247 ± 2	288 ± 26†
ATERP	56 ± 7	68 ± 7	80 ± 5*	96 ± 12†	128 ± 8	135 ± 7	147 ± 12	168 ± 14†
ATFRP	83 ± 3	93 ± 3	104 ± 5	132 ± 18†	156 ± 7	175 ± 5	182 ± 8	204 ± 9†
VERP	132 ± 3	142 ± 5	155 ± 8	168 ± 9†	153 ± 8	163 ± 3	173 ± 6	193 ± 9†
VFRP	147 ± 3	160 ± 7	174 ± 9	185 ± 10†	178 ± 5	178 ± 3	193 ± 7	215 ± 7†

All data are expressed in milliseconds (except %SNRT), mean ± standard error.
* Significant difference ($p < 0.05$), neonate versus adult.
† Significant dose-related increase ($p < 0.05$).
ATERP = atrial effective refractory period; ATFRP = atrial functional refractory period; CSNRT = corrected sinus node recovery time; %SNRT = percent sinus node recovery time; VERP = ventricular effective refractory period; VFRP = ventricular functional refractory period.

Rapid atrial pacing, programmed atrial extrastimulation and programmed ventricular extrastimulation tests were performed in all dogs. Rapid atrial pacing was performed at rates of 200 to 400 beats/min (that is, paced cycle lengths of 300 to 150 ms) at 50-beats/min increments until Wenckebach periodicity was recorded. Atrial and ventricular extrastimulation tests were performed coupled to an identical fixed paced cycle length in each dog. The mean paced cycle length for performing extrastimulation tests in the neonatal group was 251 ms and in the adult group, 359 ms. The basic driving rhythm and extrastimuli were delivered by a programmable digital stimulator (Medtronics model 5325). Atrial and ventricular extrastimuli were coupled to the eighth paced beat and delivered at 10-ms decrements until either atrial or ventricular refractoriness was reached. Stimuli were delivered bipolar, at twice threshold and with a pulse duration of 2 ms.

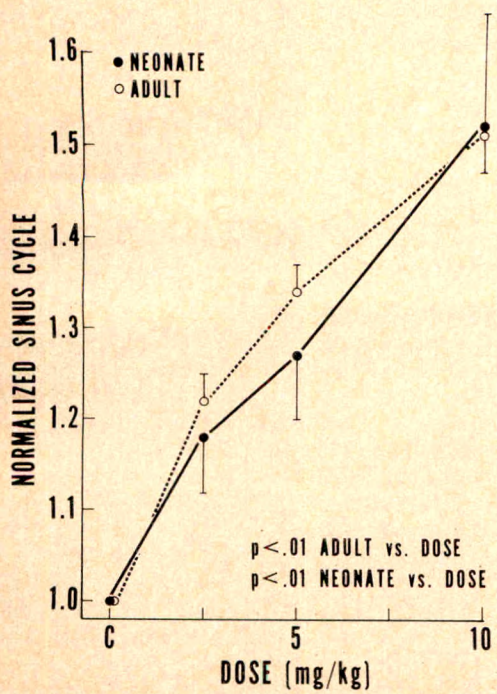

FIGURE 1. The normalized change in sinus cycle length plotted as a function of cumulative amiodarone dose. For both the neonate and the adult, a significant and similar dose-dependent increase occurs.

In this report, S_1, A_1, H_1 and V_1 refer to the pacing spike artifact, atrial, His bundle and ventricular electrogram of the basic paced rhythm, and S_2, A_2, H_2 and V_2 refer to corresponding events recorded with the extrastimulus. Electrophysiologic measurements were performed according to standard definitions[14] and are summarized as follows: effective refractory period of the atrium = the longest S_1S_2 that fails to result in atrial depolarization; functional refractory period of the atrium = the shortest A_1A_2 in response to any S_1S_2; effective refractory period of the ventricle = the longest S_1S_2 that fails to produce a V_2; functional refractory period of the ventricle = the shortest V_1V_2 in response to any S_1S_2 interval.

The percent sinus node recovery time (%SNRT) and corrected sinus node recovery time (CSNRT) were calculated according to standard methods[14] after rapid atrial pacing for 30 seconds at progressively higher rates (200 to 400 beats/min at 50-beat/min increments).

In each dog, the complete electrophysiologic protocol (which was usually completed in 20 to 30 minutes) was performed before drug administration and served as the control study. This formed the basis of assessing the effects of amiodarone. After completing the control study, 2.5 mg/kg of amiodarone hydrochloride (Labaz Laboratories) diluted in sterile water was administered intravenously. After 10 minutes to allow for drug distribution, the entire electrophysiologic protocol was repeated. After completing this study, and at a time not to exceed 45 minutes after the preceding dose, a second 2.5-mg/kg dose was administered (cumulative 5 mg/kg) and the protocol was repeated. Finally, a 5-mg/kg dose was administered (cumulative dose 10 mg/kg) and a complete electrophysiologic assessment was performed.

Statistical analyses of the effects of dose on a given electrophysiologic parameter in each age group was performed by an analysis of variance. Comparisons of paired data between adult and neonatal groups at specific dosage levels was performed by a Student t test. In all statistical analyses, a p value <0.05 was required to indicate significance. Data used to compare the electrophysiologic responses of the adult and neonate are normalized to account for inherent differences in heart rate and refractoriness: normalized value = observed value/control value.

Results (Table I)

Sinus cycle length and sinus node recovery time: In both the neonatal and adult groups, amiodarone produced significant dose-dependent changes in the sinus cycle length (Fig. 1). In the adult group, an overall increase in sinus cycle length of 51% was observed across the entire dosing interval. In the neonate, a clear dose-dependent increase of sinus cycle length was observed (274 ± 7 ms control to 410 ± 33 ms); this was, on a percentage basis (52%), comparable to that in the adult.

Changes in %SNRT were small in both the adult and neonatal groups (Fig. 2), which reflects primarily the proportional prolongation of SNRT and sinus cycle length by amiodarone. The depressant effects of amiodarone on sinus node function was better observed by considering the CSNRT (Fig. 2). In the neonate, a dose-dependent increase in CSNRT was observed, with an overall mean increase of 115 ± 37%. Sinus node function in the neonates as measured by CNSRT tended to show more depression with amiodarone than that in the adult (normalized CSNRT—1.78 ± 0.17 neonate, 1.13 ± 0.14 adult at 5-mg/kg dose level; $p < 0.02$).

Resting His intervals and atrioventricular nodal function: No significant changes in either the PA or the HV intervals were observed in either the neonatal or adult groups over the entire dosing protocol (Table I). However, as reported in other studies, amiodarone produced a significant change in AV nodal conduction in the adult as measured by both the resting AH interval and the paced cycle length at which AV nodal Wenckebach periodicity was observed.

In the adult group, the AH interval was prolonged by 42% over the dosage range and the paced cycle length at which Wenckebach was observed in the AV node increased by 49% (Fig. 3 and 4). In the neonate, a mean increase was observed in the resting AH interval of only 16% over the entire dosing range and of only 34% in the paced cycle length resulting in AV nodal Wenckebach (Fig. 3 and 4). Thus, conduction through the AV node appeared to be depressed to a lesser extent by amiodarone in the neonate than in the adult.

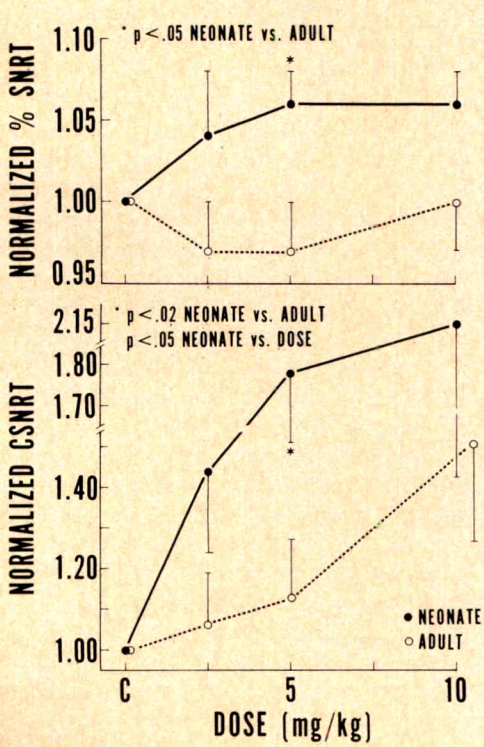

FIGURE 2. The normalized percent sinus node recovery time (% SNRT) and corrected sinus node recovery time (CSNRT) plotted as a function of amiodarone dose. Although no clear dose-dependent increase in % SNRT is evident, the CSNRT increases significantly in the neonate

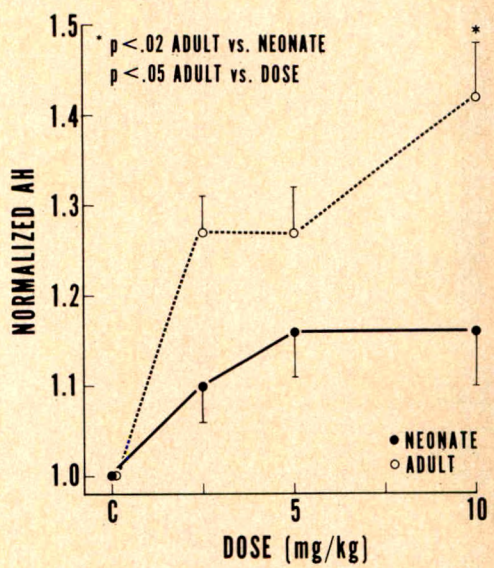

FIGURE 3. Normalized change in AH interval plotted as a function of amiodarone dose for the neonate and adult. The AH interval in the adult is prolonged to a greater degree than in the neonate.

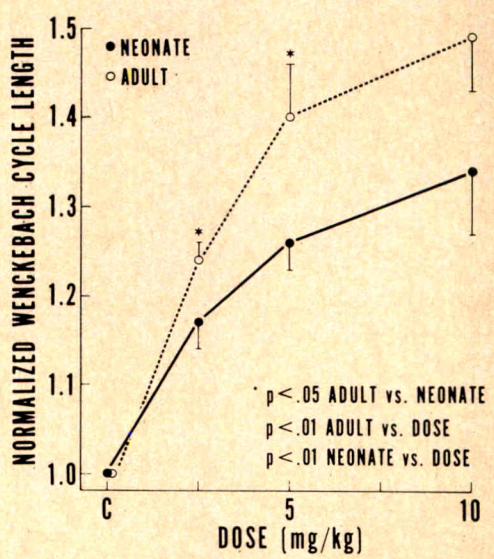

FIGURE 4. Normalized paced cycle length resulting in Wenckebach periodicity in the neonate and adult groups plotted as a function of amiodarone dose. As shown for the AH interval, atrioventricular nodal conduction is more significantly depressed by amiodarone in the adult

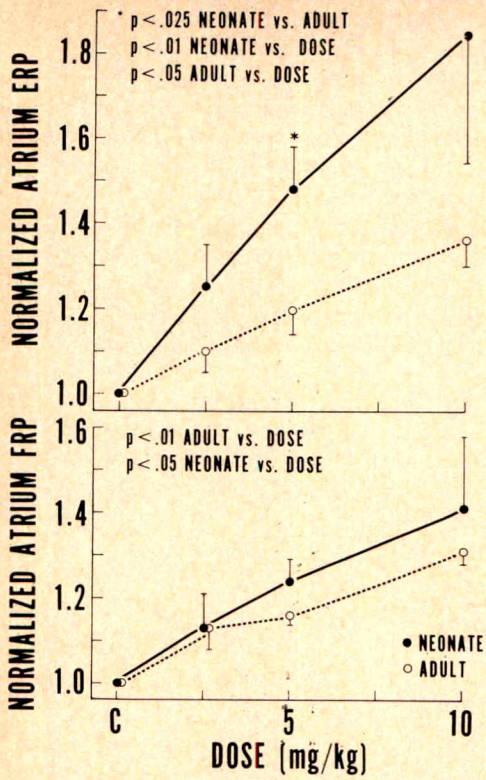

FIGURE 5. Normalized atrial effective refractory period (ERP) and atrial functional refractory period (FRP) plotted against amiodarone dose. Dose-dependent increases occur in both the neonatal and the adult group. The neonatal atrium appears to be more sensitive than the adult atrium to amiodarone.

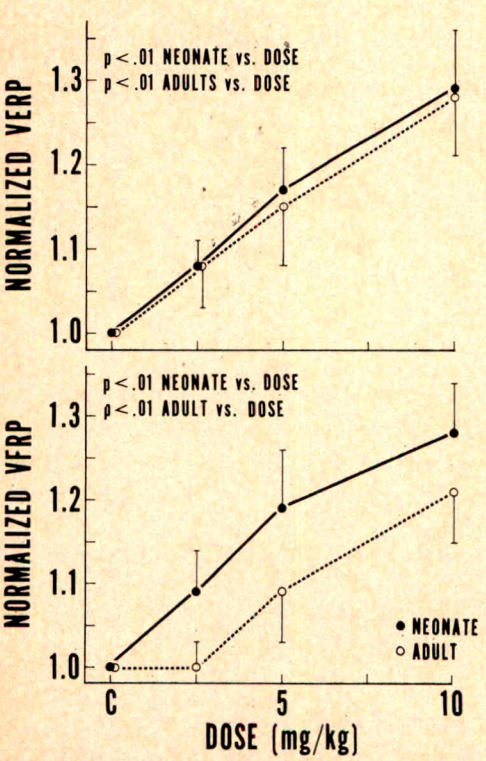

FIGURE 6. Normalized ventricular effective and functional refractory periods (VERP and VFRP) versus amiodarone dose. Similar dose-dependent increases occur in the neonatal and the adult group.

Atrial refractory periods: Amiodarone produced dose-dependent increases in both the atrial effective and functional refractory periods in the adult and neonatal groups (Fig. 5). Amiodarone appeared to prolong the atrial refractory periods (particularly the effective refractory period) to a significantly greater degree in the neonatal group. Thus, the 35% change in the atrial effective refractory period in the adult produced by the highest amiodarone dose would be achieved in the neonate at a much lower dose of 2.5 to 5 mg/kg (Fig. 5). Similarly, the changes in the functional refractory period of the atrium tended to be greater in the neonatal group than in the adult group (1.41 ± 0.17 in the neonate versus 1.31 ± 0.03 in the adult). Thus, the neonatal atrium was apparently more sensitive (that is, a greater percent change in refractory periods) than the adult to intravenous amiodarone.

Ventricular refractory periods: Ventricular refractory periods increased in a dose-dependent fashion in both the neonatal and adult groups (Fig. 6). The effective refractory period increased a mean of 29% in the adult and 28% in the neonatal group over the entire dosage range, and the functional refractory periods increased in parallel and to a similar degree (28% in the adult and 21% in the neonate). Thus, amiodarone appeared to be equipotent in both groups in prolongation of ventricular refractory periods.

Discussion

In this study, we have defined the electrophysiologic effects of intravenous amiodarone in the intact immature mammalian heart. Our data demonstrate that amiodarone produces significant dose-dependent increases in sinus cycle length, CSNRT, and atrial and ventricular refractory periods. Amiodarone also produces dose-dependent suppression of AV nodal conduction in the immature heart, but this suppression is primarily evident only when the AV node is "stressed" by rapid atrial pacing. These observations in the neonate are similar to the electrophysiologic dose-response curves in the adult dog in the present study and in that of Jaillon et al[9] (Table II). In humans, however, although AV nodal depression has been uniformly reported after amiodarone administration, changes in sinus rate and atrial and ventricular refractory periods have been variable. Although this may in part be explained by species differences, differences in autonomic tone or differences in methods of sedation for electrophysiologic study, we believe that some of these discrepancies may be related to the fact that in human subjects, only single-dose studies have been performed to assess the electrophysiologic effects of amiodarone. To completely characterize an agent's electrophysiologic responses, multidose studies are more likely to reveal information concerning the effects of a given drug.

Of particular interest to the pediatric cardiologist is the relative responsiveness of the immature myocardium to antiarrhythmic agents. Both clinical and microelectrode studies provide convincing evidence that important quantitative differences exist in the re-

TABLE II Electrophysiologic Effects of Intravenous Amiodarone in the Mature Mammalian Heart

Study	Species	Dose (mg/kg)	Sinus Node	Atrium	AV Node	HV	Ventricle
Touboul et al, 1976[10]	Man	5	↓ rate	↑ ERP	↑ AH ↑ ERP ↑ FRP	no Δ	↑ ERP
Cabasson et al, 1976[11]	Dog	10	↓ rate	↑ERP ↑ FRP	↑ AH	no Δ	↑ ERP
Touboul, 1979[19]	Man	5	↑ CSNRT	. . .	. . .	. . .	. . .
Wellens et al, 1982[13]	Man	5	↑ rate	no Δ	↑ AH ↑ ERP	no Δ	no Δ
Brugada et al, 1982[12]	Man	5	no Δ	no Δ RA ↑ ERP/LA ↑ FRP/LA	↑ AH ↑ ERP ↑ FRP	. . .	no Δ
Jaillon et al, 1982[9]	Dog	1.25–10	↓ rate	↑ ERP ↑ FRP	↑ FRP	no Δ	↑ ERP

AV = atrioventricular; CSNRT = corrected sinus nodal recovery time; ERP = effective refractory period; FRP = functional refractory period; LA = left atrium; No Δ = no change; RA = right atrium; ↑ = increase.

sponses of the immature mammalian heart to various antiarrhythmic drugs and that both increased sensitivity and decreased sensitivity can be found.[15–18] In the present study, amiodarone had measurable age-related differences in its effect upon CSNRT, atrial refractoriness and AV nodal conduction. Concerning the sinus node, although the sinus cycle length is prolonged in both the adult and neonate to a similar extent by amiodarone, sinus node function as measured by CSNRT is prolonged more by amiodarone in the neonate. We have also found that the neonatal atrium appears to be more sensitive (that is, a greater percent increase in refractory periods) than the adult atrium to amiodarone.

In contrast to the increased sensitivity of the neonatal sinus node and atrium, this study indicates that amiodarone-induced depression of AV nodal conduction is more marked in the adult than in the neonate. Thus, higher doses of amiodarone may be required in the neonate to produce a degree of change in AV nodal conduction similar to that in the adult.

Whether the differences we observed in the responses of the neonate and adult to amiodarone reflect changes with age in the status of the autonomic nervous system, inherent differences in the ionic mechanisms responsible for the generation of the neonatal action potential, or other undetermined factors is not addressed by this study. Furthermore, we do not know how the results of this study would be altered if diseased hearts (instead of normal hearts) had been studied. Nevertheless, this report suggests that important differences may exist in the manner in which the immature heart responds to intravenous amiodarone. These differences may prove to be of clinical importance in the formulation of a rational approach to amiodarone therapy in the immature human being.

Acknowledgment: We thank Diane McMullen for secretarial assistance.

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Protection of Turkeys Against Furazolidone-Induced Cardiomyopathy

JUDITH K. GWATHMEY, VMD and ROBERT L. HAMLIN, DVM, PhD

When fed furazolidone, 700 ppm, with their mash, most turkey poults develop dilated cardiomyopathy characterized by gross left ventricular dilatation with thinning of both the left ventricular free wall and ventricular septum. Birds fed propranolol, but not digoxin, did not develop this cardiomyopathy. It is not known what pharmacologic property of propranolol conferred protection or if mammals would receive similar protection.

(Am J Cardiol 1983;52:626–628)

Turkey poults fed 700 ppm of furazolidone develop dilated cardiomyopathy (DC) within 2 weeks.[1–3] Because turkey poults develop DC spontaneously,[4] it is not known whether furazolidone produces DC or merely potentiates it. DC in turkeys is characterized by ventricular dilatation, premature death and ascites. The clinical findings mimic quite closely those in mammals with DC.

How furazolidone produces cardiomyopathy in turkeys is unknown; however, certain biochemical observations suggest that the compound may inhibit the conversion of pyruvate to acetyl coenzyme A.[5] Studies by others have shown elevation of both lactate and pyruvate in turkeys treated with furazolidone. Further, significant increases in myocardial glycogen levels in both furazolidone-induced cardiomyopathy and spontaneous round heart disease have been observed. Enzyme inhibition of the glycogen metabolic pathway by furazolidone raises the possibility that the spontaneous heart condition that resembles furazolidone-induced cardiomyopathy represents a manifestation of glycogen storage disease. Abnormal accumulation of glycogen in heart and skeletal muscle is similar to that reported in sheep and dog with idiopathic glycogenolysis. In these cases, as in Pompe's disease in man, an enlarged heart was a characteristic finding. Other similarities include a familial occurrence, early onset in life, anorexia, cyanosis, dyspnea, failure to grow and a tendency toward sudden death when an affected animal is stressed.[5] Morphologic alterations such as loss and disarray of myofilaments, accumulation of cytoplasmic glycogen and mitochondrial changes observed in the drug-induced cardiomyopathy in turkey poults are similar to those in a number of mammalian species.[2,5]

Prophylaxis against or therapy for DC is sought because of the prevalence and catastrophic consequences; beta-adrenergic blocking agents and digitalis have been proposed for both.[6] The purpose of this study was to determine if propranolol or digitalis protects turkey poults against the development of DC when fed furazolidone.

Methods

Ninety 7-day-old broad-breasted white turkey poults were separated into 6 groups of 15 turkeys per group. One group received only a commercial mash and served as a control, and other groups received, in addition, 1 of the following: (1) furazolidone, 700 ppm, ad libitum in commercial mash; (2) furazolidone (as in 1) plus digoxin* orally, 0.0025 mg/100 g, daily; (3) furazolidone (as in 1) plus propranolol* orally, 1 mg/100 g, 3 times a day; (4) propranolol; and (5) digitalis.

The turkeys were fed the above for 2 weeks, after which they were killed. Body weights and heart weights were measured to permit calculation of heart weight:body weight ratios. After hearts were fixed in formalin for 3 weeks, median sagittal sections were cut through them and the sections were photographed and amplified equally. Hearts fixed for >3 months return to a volume nearly identical to that immediately after death.[7] From the photographs, the following measurements were made at right angles to the long axis of the heart and midway between the apex and base: left ventricular (LV) free-wall thickness; LV luminal diameter; LV luminal length; and ventricular septal thickness.

Means for each variable for each group were calculated, and when indicated by a suitable F statistic (analysis of variance),

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* These doses gave blood levels of 15 to 100 ng/ml for propranolol and 0.8 to 2.7 ng/ml for digoxin.

TABLE I Means (± Standard Error) for Variables Measured or Calculated for Groups of Turkeys

	Heart Weight / Body Weight	LV Free Wall (mm)	Ventricular Septum (mm)	Diameter of LV Cavity (mm)	Length of LV Cavity (mm)
Control	0.7* (0.02)	5* (0.39)	4* (0.43)	7* (0.41)	29* (1.44)
Propranolol	0.7* (0.04)	6* (0.56)	5* (0.38)	5* (0.95)	27* (1.03)
Digoxin	0.7* (0.02)	5* (0.71)	5* (0.43)	6* (0.95)	26* (1.38)
Furazolidone	1.4† (0.14)	2† (0.13)	2† (0.19)	20† (1.47)	34† (2.27)
Furazolidone + propranolol	0.7* (0.10)	4* (0.66)	4* (0.34)	7* (1.49)	23* (1.55)
Furazolidone + digoxin	1.1† (0.09)	3† (0.14)	2† (0.25)	20† (1.93)	34† (1.29)

* Did not differ significantly from others marked with an asterisk.
† Did not differ significantly from others marked with a dagger.
LV = left ventricular.

they were compared by Newman-Keul's, with $p < 0.05$ considered significantly different.

Results

All turkeys survived the 2-week feeding. Figure 1 shows hearts typical of all groups. Turkeys that received furazolidone and furazolidone plus digitalis—but no others—showed remarkable dilatation of the left ventricle and thinning of the LV free wall and ventricular septum. Hearts from these turkeys occupied the greater portion of the thorax at postmortem examination.

Table I shows means for all variables measured. For each variable, means for turkeys that received either furazolidone or furazolidone plus digitalis did not differ between these 2 groups. For each variable, means from the first cluster (of 2) were different from means of the second cluster (of 4). Thus, furazolidone produced remarkable LV dilatation, neither digitalis nor propranolol alone caused any change, and propranolol prevented but digitalis did not prevent the dilatation when fed with a dose of furazolidone that produces this cardiomyopathy.

Discussion

This study shows that propranolol, but not digitalis, prevents LV dilatation and free wall thinning produced by furazolidone in turkey poults. We do not know if the mechanism by which furazolidone produces cardiomyopathy is analogous to that by which birds develop the disease spontaneously or, even if the mechanisms were identical, whether propranolol would deter or completely block the development in mammals.

Furthermore, propranolol possesses many properties (for example, beta blockade, platelet inhibition, calcium-channel blockade and membrane stabilization), so we do not know what property of this compound prevents ventricular dilatation.

Swedberg,[6] Waagstein,[8] and their co-workers showed that reduction of beta-adrenergic drive prolonged the lives of human patients with dilated cardiomyopathy. The survival rate in 24 patients with severe failure was 83, 66 and 52% after 1, 2 and 3 years, respectively. In a comparable group of patients who were treated without beta blockers, the survival rate was 46, 19 and 10%. They

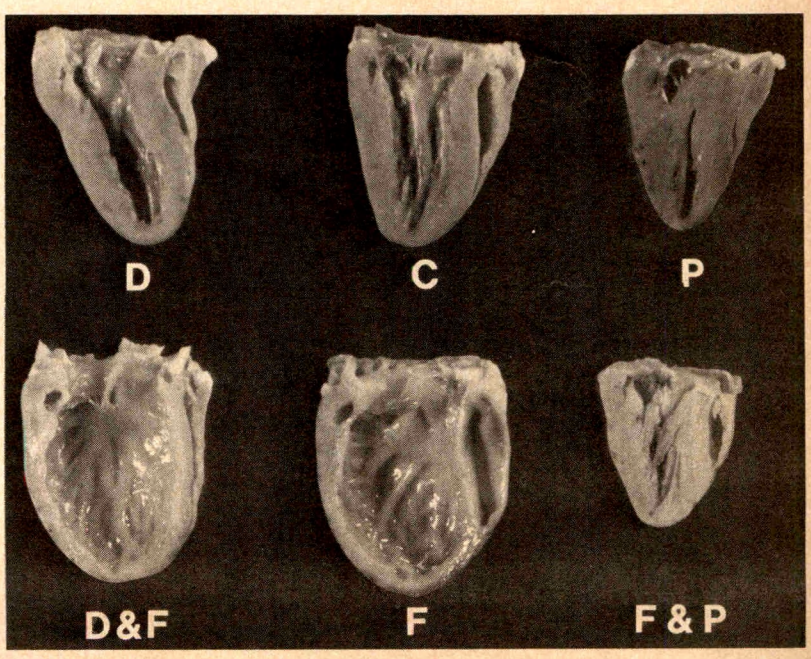

FIGURE 1. Hearts from each of the 6 treatment groups. **Top,** hearts from digoxin (D)-, control (C)- and propranolol (P)- treated turkeys. **Bottom,** hearts from turkeys that received digoxin plus furazolidone (D & F), furazolidone (F), and furazolidone plus propranolol. (F & P).

demonstrated objective indications of improved LV function and less ventricular dilatation. Findings indicated a decrease in LV end-diastolic diameter, an increase in ejection fraction and an increase in LV ejection time indicating an increased stroke volume. Therefore, improved myocardial function with chronic beta blockade could improve prognosis. They suggested that reduction in heart rate by partial beta blockade—similar to what results from bedrest—may be a partial explanation for the beneficial effects of propranolol. It was also found that withdrawal of treatment caused a deterioration of myocardial function and, in several patients, led to distinct exacerbation of their symptoms.[9]

Thus, cardiac deterioration may result primarily from a primary insult (for example, viremia, adriamycin, alcohol or cobalt) and secondarily from excessive drive by catecholamines, and the reduction in beta-adrenergic drive by blocking agents may save the heart from the adversity of excessive adrenergic drive.

Bristow et al[10] reported that beta-receptor density is reduced greatly in failing human hearts and that these hearts are less responsive to catecholamines. Motulsky and Inset[11] proposed that the reduced beta-receptor activity may have resulted from sustained elevation of catecholamines. Thus, since propranolol should abolish or reduce the effects of elevated catecholamines, population of beta-adrenergic receptors may not be reduced, and potential for changes in myocardial contractility mediated by beta receptors may not be abolished.

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Mechanism of Calcification of Porcine Bioprosthetic Aortic Valve Cusps: Role of T-Lymphocytes

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Calcification of glutaraldehyde-preserved porcine aortic valve bioprosthetic cusps limits their success as cardiac valve substitutes. Subcutaneous implants of porcine bioprostheses in rats and rabbits have provided a convenient experimental tool to study this calcification process. Previous clinical research has suggested that the host's immune response to the porcine xenograft tissue may contribute to the calcific degeneration. To investigate the possible contribution of the immune response, porcine bioprosthetic cusps implanted subcutaneously in congenitally athymic (nude) BALBc mice and normal controls were analyzed biochemically and histologically after retrieval at 21 days. Calcification was comparable in implants retrieved from athymic (calcium 95.5 ± 24.5 μg/mg) and normal mice (calcium 102.3 ± 4.66 μg/mg). Explants from nude mice demonstrated fewer adherent cells than those from normal animals, but the morphologic characteristics of the calcification were the same in both groups, with dystrophic mineralization of the spongiosa predominating. Thus, normal T-lymphocyte function is not necessary for porcine bioprosthetic calcification, and immunologic processes do not contribute to this process.

(Am J Cardiol 1983;52:629–631)

Bioprosthetic cardiac valves fabricated from glutaraldehyde-preserved porcine aortic valve xenografts are widely used for cardiac valve replacement.[1–5] Late calcification of porcine bioprostheses frequently leads to their failure due to cuspal stiffening or tearing.[6–8] The host's immune response to the xenograft tissue has been considered by some investigators to play a role in the pathogenesis of the calcification.[9–11] Calcification of porcine bioprotheses has been studied by implanting porcine aortic valve cusps subcutaneously in rabbits[12] and rats.[13] After several weeks in rats[13] and several months in rabbits,[12] experimental implants demonstrate morphologic and biochemical abnormalities similar to those implanted in the heart.[12,13]

Nude mice are congenitally athymic and have a grossly defective immune system due to deficiencies in T-cell–dependent immunologic processes. These mice have a virtual absence of T-lymphocytes[14,15] and therefore lack T-cell effector functions, including delayed hypersensitivity and rejection and facilitation of antibody formation. In the present study, the hypothesis that T-lymphocytes may play a role in calcification of porcine bioprostheses was examined by comparing subcutaneous porcine bioprosthetic cusps implanted in congenitally athymic (nude) mice with those implanted in normal mice.

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Methods

Porcine bioprosthetic cusps were prepared according to the methods of Carpentier et al,[1] and were stored at room temperature in 0.2% glutaraldehyde solution, buffered to pH 7.4 in 0.05 *M* $Na_2H_2PO_4$, 0.9% NaCl. Three-week-old male BALBc nude mice and normal BALBc male mice obtained from Charles River Laboratories received subcutaneous implants according to established techniques.[12,13] The mice were maintained in laminar flow enclosures with filter-capped cages. Drinking water was passed through Millipore filters, and lab chow (Ralston-Purina) feedings were autoclaved. No mice had overt infections during the course of the experiments. Twenty-one days after implantation, blood sampling was done by cardiac puncture. The mice were then killed and the valve cusps retrieved.

A portion of each cusp was immediately fixed in 0.1 *M* cacodylate-buffered (pH 7.4) 2.5% glutaraldehyde, 2% paraformaldehyde solution. Histologic specimens were subsequently dehydrated in graded alcohols, embedded in glycolmethacrylate medium (JB-4, Polysciences), sectioned at 2 to 3 μm and stained with hematoxylin-eosin for general mor-

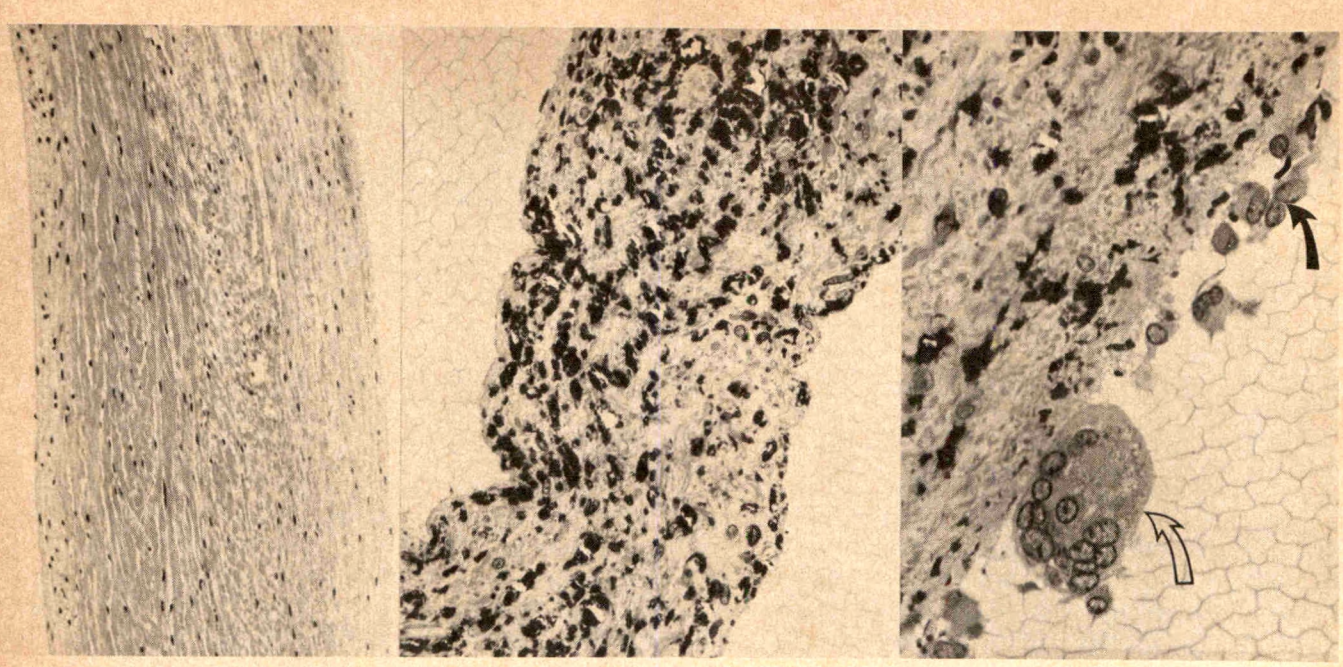

FIGURE 1. Cross-sectional photomicrographs of glutaraldehyde-preserved porcine aortic bioprosthetic cusps. **Left,** unimplanted; **center,** implanted 3 weeks in nude mouse; **right,** implanted 3 weeks in BALBc mouse, control for nude. Dense black patches in **center** and **right panels** are deposits of calcium phosphate mineral. Note mononuclear inflammatory cells (**closed arrow**) including multinucleated giant cell (**open arrow**) at surface of valve shown in the **right panel,** and the absence of those cells at the surface of the valve illustrated in the center panel. Hematoxylin-eosin stain; magnification ×150 (**left**), ×375 (**center**), ×600 (**right**), reduced 23%.

phology and by von Kossa's method for calcium-phosphate. Cell attachment to the surface of the retrieved bioprosthetic leaflets was assessed semiquantitatively as none (0), rare (1+), few (2+) or many (3+). Retrieved leaflets were milled under liquid nitrogen to a coarse powder and dried to constant weight in a vacuum dessicator. Then, 6 N-HCl hydrolysates of bioprosthetic specimens were analyzed for calcium levels by atomic absorption,[12] and for phosphorus levels by the method of Chen et al.[16] Calcium and phosphorus levels were also quantitated in the mouse serums using the same methods. Data were assessed statistically using a Student t test.

Results

The bioprosthetic cusps retrieved from both athymic and normal mice were grossly thickened and calcified to a similar degree. Microscopic calcification was similar morphologically in the bioprosthetic cusps from the nude and normal mice (Fig. 1). By light microscopy, there was a diffuse pattern of calcific deposits, ranging from 5 to 50 μm, many of which were clearly associated with residual, devitalized porcine valve nuclei. No host cell penetration was noted. Although retrievals from normal mice had adherent cells (principally macrophages) ranging from rare to many, there was markedly diminished cellular adherence to the porcine bioprosthetic tissue in the nude mouse explants with none to rare cells attached (Fig. 1).

Biochemical analyses of porcine bioprosthetic cusp retrievals (Table I) revealed increased calcium and phosphorous content in those retrieved from both nude and normal mice compared with the unimplanted bioprosthetic cusps. No statistically significant differences were noted in valvular calcium and phosphorus content between porcine bioprosthetic cusps retrieved from athymic and those from normal mice. Serum calcium and phosphorus levels were also not significantly different between the 2 groups.

Discussion

Calcification of glutaraldehyde-preserved porcine aortic valve cusps, previously studied subcutaneously in rabbits[12] and rats,[13] has morphologic and biochemical features analogous to those seen in clinical explants

TABLE I Xenograft Valve Nude Mouse Studies

Implant Experiment	n	GPV Calcium (μg/mg)	GPV Phosphorus (μg/mg)	Serum Calcium (mg/dl)	Serum Phosphorus (mg/dl)
BALBc normals	15	102 ± 4.7	53 ± 2	7.2 ± 0.3	8.0 ± 0.6
BALBc nudes	9	96 ± 25	54 ± 13	8.1 ± 0.2	8.4 ± 0.3
Unimplanted valve leaflets	7	2.8 ± 0.7	2.5 ± 0.5	. . .	. . .

Values expressed as mean ± standard error.

after several years.[17] Experimental degenerative calcification of porcine bioprosthetic cusps is dependent on the glutaraldehyde pretreatment of the valve cusps, is more severe in younger animals and is apparently independent of host inflammatory cell attachment.[13] The present study indicates that subcutaneous calcification of porcine bioprosthetic cusps also occurs in the mouse, which has a morphology and biochemistry similar to that previously observed both clinically and experimentally.

The primary result of this study is that calcification of porcine bioprosthetic cusps was identical in congenitally athymic (nude) mice and controls. A role of the immune response in porcine bioprosthetic calcification has been previously suggested. Several cases of porcine bioprosthetic xenograft valve failure associated with immunologic rejection have been reported.[10,11] Rocchini et al[9] demonstrated both a humoral and cellular immune response to porcine xenograft valve replacements in a large clinical series, including several cases of calcification. A number of the cases reported by Rocchini et al[9] had plasma hypergammaglobulinemia and plasmacytosis. Porcine bioprosthetic immune complex deposition and cellular infiltration with lymphocytes and macrophages were also described. Although it is not clear whether the immune processes were primary or secondary, these investigators proposed a mechanism whereby bioprosthetic tissue damage secondary to the immune response may lead to valvular calcification. Experimental induction of both humoral[18] and cellular[19] immune responses elicited to subcutaneous porcine bioprosthetic implants has been observed by Bajpai and his co-workers. Neither of these studies, however, specifically examined whether the immune response to the porcine bioprosthetic xenografts had a cause-and-effect relationship to the calcification.

Our results show that experimental calcification of porcine bioprosthetic xenograft tissue does not require normal T-lymphocyte activity, and suggest that calcification is not caused by immunologic phenomena. However, the results of the present study do not eliminate the possibility that immunologic reactions to the xenograft tissue may be of pathogenetic importance to the ubiquitous collagen deterioration and degenerative processes other than calcification in long-term porcine bioprosthetic circulatory implants.[6–8]

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Formation of Cartilage in Bioprosthetic Cardiac Valves Implanted in Sheep: A Morphologic Study

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Foci of cartilage were found in 12 of 120 bioprostheses implanted in young sheep for 13 to 24 weeks, but in none of 47 bioprostheses implanted for <13 weeks. Cartilage was found more frequently ($p < 0.01$) in bioprotheses implanted in the tricuspid position than in those implanted in the mitral position. In porcine aortic valvular bioprostheses, the cartilage was preferentially localized in the region of the muscle shelf; in pericardial bioprostheses, it occurred in the fibrous sheaths covering the cusps. In both instances, the cartilage was found to undergo calcification and was considered to be formed by metaplasia of connective tissue cells of host origin. **(Am J Cardiol 1983;52:632–636)**

Although many pathologic conditions, such as infection, fibrous sheathing, thrombosis and tissue degeneration, can be responsible for dysfunction of cardiac valvular bioprostheses, mineralization of connective tissue represents the most common cause of bioprosthetic dysfunction.[1,2] Cellular mechanisms of calcification have been previously considered not involved in the formation of calcific deposits in bioprosthetic cuspal tissue because the native cells of bioprosthetic valves are killed by the commercial preimplantation process with glutaraldehyde.[3] In addition, connective tissue cells of host origin have not been found to participate in the calcification of bioprosthetic connective tissue. Nevertheless, we recently found nodules of calcifying hyaline cartilage in cusps of porcine aortic valvular bioprostheses and bovine pericardial bioprostheses explanted from experimental animals. This report describes the incidence, location and morphology of these nodules, and proposes an additional mechanism for the process of mineralization of bioprostheses.

Methods

The study material consisted of 167 bioprostheses (Table I) recovered after implantation in young sheep, either in the tricuspid or in the mitral position, according to procedures previously described.[4] The explants were considered to be early if the bioprostheses had been in place for <6 weeks and late if they had been in place for >6 weeks. Forty-seven explants were early (34 explanted from the mitral position and 13 from the tricuspid position) and 120 were late (40 explanted from the mitral position and 80 from the tricuspid position). After explantation, the bioprostheses were examined grossly, photographed and radiographed. Each cusp was then detached from the stent and divided into 2 halves. One half was submitted for quantitative analysis of calcium using atomic absorption spectrophotometry; the other was subdivided into 3 portions that were used for histologic, transmission electron microscopic and scanning electron microscopic studies.[5]

TABLE I Incidence of Cartilage in Various Types of Bioprosthetic Valves Explanted From Sheep

Type of Valve	Position	Early Explants		Late Explants	
		Cartilage	Total	Cartilage	Total
Ionescu-Shiley	Mitral	0	9	1	11
BPB-Std	Tricuspid	0	3	0	11
Ionescu-Shiley	Mitral	0	1	0	0
BPB-TR	Tricuspid	0	0	1	8
Hancock	Mitral	0	10	0	6
PAB-Std	Tricuspid	0	1	3	8
Hancock BPB-Std	Tricuspid	0	0	1	9
Hancock PAB-TR	Tricuspid	0	0	3	9
Hancock BPB-TR	Tricuspid	0	3	2	6
Xenotech	Mitral	0	0	0	6
PAB-TR	Tricuspid	0	1	1	6
Xenotech	Mitral	0	3	0	7
PAB-Std	Tricuspid	0	0	0	6
Dura mater	Tricuspid	0	2	0	5
Carpentier-Edwards	Mitral	0	11	0	10
PAB-Std	Tricuspid	0	3	0	12
Total		0	47	12	120

BPB = bovine pericardial bioprostheses; PAB = porcine aortic valvular bioprosthesis; Std = standard; TR = anticalcification treatment.

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Results

Incidence of hyaline cartilage in early and late explanted bioprostheses: Hyaline cartilage was not observed in any of the 47 early explants. Hyaline cartilage was found in 16 cusps from 12 of the 120 late explants (10%) (Tables I and II). Seven affected valves were porcine aortic valvular bioprostheses, including 3 standard (not treated with an anticalcification process) Hancock valves, 3 anticalcification-treated (T6 process) Hancock valves, and 1 anticalcification-treated Xenotech valve. The other 5 were pericardial valves, including 1 standard Hancock valve, 2 T6 process Hancock valves, 1 anticalcification-treated Ionescu-Shiley valve and 1 standard Ionescu-Shiley valve. Only 1 of these bioprostheses (a standard Ionescu-Shiley pericardial valve) was explanted from the mitral position; the other 11 were explanted from the tricuspid position (Tables I and II). In late explants, the incidence of hyaline cartilage was 3% in mitral bioprostheses and 14% in tricuspid bioprostheses. These 2 incidences are significantly ($p < 0.01$) different (chi-square method).

Roentgenographic studies: Calcific deposits were detected radiographically in 9 of the 12 valves in which cartilage was found (Table II). The other 3, which were T6-treated Hancock valves, had no radiographic evidence of calcific deposits; however, on histologic examination these 3 valves were found to have very small calcific deposits.

Quantitative calcium analyses: The amounts of calcium present in the cusps of the explanted bioprostheses are shown in Table II. These amounts varied from 1.5 ± 1.4 to 110 ± 35 mg of calcium per gram of tissue dry weight; they did not show a significant correlation with the presence of cartilage, although most of the values were greatly in excess of those in unimplanted valves (<1 mg/g).[4]

Histologic observations: Cartilage was identified in 8 cusps from 7 porcine bioprostheses and 7 cusps from 5 pericardial bioprostheses (Table II). In each of the porcine bioprostheses, cartilage was present in the muscle shelf (Fig. 1A to C); in another cusp of 1 of these valves, cartilage was also found in the fibrous sheath at the base of the cusp.

In 7 cusps from 5 pericardial bioprostheses (Fig. 1D and E), cartilage was located in the fibrous sheath (in the basal third of the cusp in 4, the middle third in 2, and the distal third in 1). Thus, cartilage was not present in pericardial valves unless fibrous sheathing had developed over the affected cusps. In no pericardial valve was the cartilage present within the thickness of the original cuspal tissue. No correlation was observed between the extent of the calcific deposits and the presence of hyaline cartilage.

The nodules of cartilage were composed of chondrocytes embedded in an amorphous matrix that stained metachromatically with toluidine blue and appeared blue in preparations stained with hematoxylin-eosin (Fig. 1E and 2A). Cells that appeared intermediate between fibroblasts and chondrocytes were frequently observed at the periphery of foci of cartilage (Fig. 1E). In 6 cusps (3 from porcine bioprostheses and 3 from pericardial bioprostheses), the foci of cartilage formation were small and consisted of a few chondrocytes embedded in small areas of matrix. In the other 9 cusps (5 from porcine bioprostheses and 4 from pericardial bioprostheses), the cartilaginous foci were more extensive and in a more advanced stage of development. In 1 valve, the chondrocytes were surrounded by calcific deposits and the metachromatic matrix had disappeared almost completely. All foci of cartilage had areas in which the von Kossa reaction for calcium was positive (Fig. 2B). If the formation of cartilage was early, the von Kossa reaction was limited to a few discrete particles; in areas in which cartilage was more extensive and organized, the reaction was more diffuse except for the presence of von Kossa-negative cellular lacunae. In some cusps, areas of metachromatic staining, similar to

TABLE II Clinical and Morphologic Findings in Sheep With Cartilaginous Foci in Implanted Bioprosthetic Cardiac Valves

Animal Number	BP type	Weeks BP in Place	BP Position	Cuspal Calcium Content (mg/g)*	Calcium on roentgenogram	Location of Calcium Deposits				Location of Cartilage	
						RCC 1†	LCC 2†	NCC 3†	Muscle Shelf	Muscle Shelf	Fibrous Sheath
1	Hancock Std PAB	24	T	87.7 ± 76	+	+	+	−	0	0	RCC
2	Hancock Std PAB	24	T	10.8 ± 1	+	+	0	−	+	RCC	0
3	Hancock Std PAB	24	T	64.6 ± 33	+	+	+	−	+	RCC‡	0
4	Hancock PAB-TR	21	T	22 ± 18	0	0	+	+	+	RCC	0
5	Hancock PAB-TR	18	T	25 ± 33	0	0	0	+	+	RCC‡	0
6	Hancock PAB-TR	21	T	1.5 ± 1.4	0	0	0	0	+	NCC	0
7	Xenotech PAB-TR	21	T	...	+	+	+	+	+	LCC‡	3
8	Hancock BPB-TR	20	T	110 ± 35	+	+	0	+	...	...	3‡
9	Hancock PBP-TR	21	T	44.1 ± 60	+	+	+	+	...	...	3‡
10	Hancock Std BPB	21	T	18.9 ± 26	0	+	+	+	...	...	3
11	Ionescu-Shiley BPB-TR	19	T	6.3 ± 4	+	+	+	+	...	...	2, 3
12	Ionescu-Shiley Std BPB	13	M	92 ± 20	+	0	+	+	...	...	3‡

* Mean value ± standard error of the mean in milligrams of calcium per gram tissue dry weight.
† Arbitrarily numbered cusps of pericardial valves.
‡ Early deposits.
BP = biprosthesis; BPB = bovine pericardial bioprosthesis; LCC = left coronary cusp; M = mitral; NCC = noncoronary cusp; PAB = porcine aortic valvular bioprosthesis; RCC = right coronary cusp; Std = standard; T = tricuspid; TR = bioprosthesis treated with anticalcification process; + = present; 0 = absent; − = data not available.

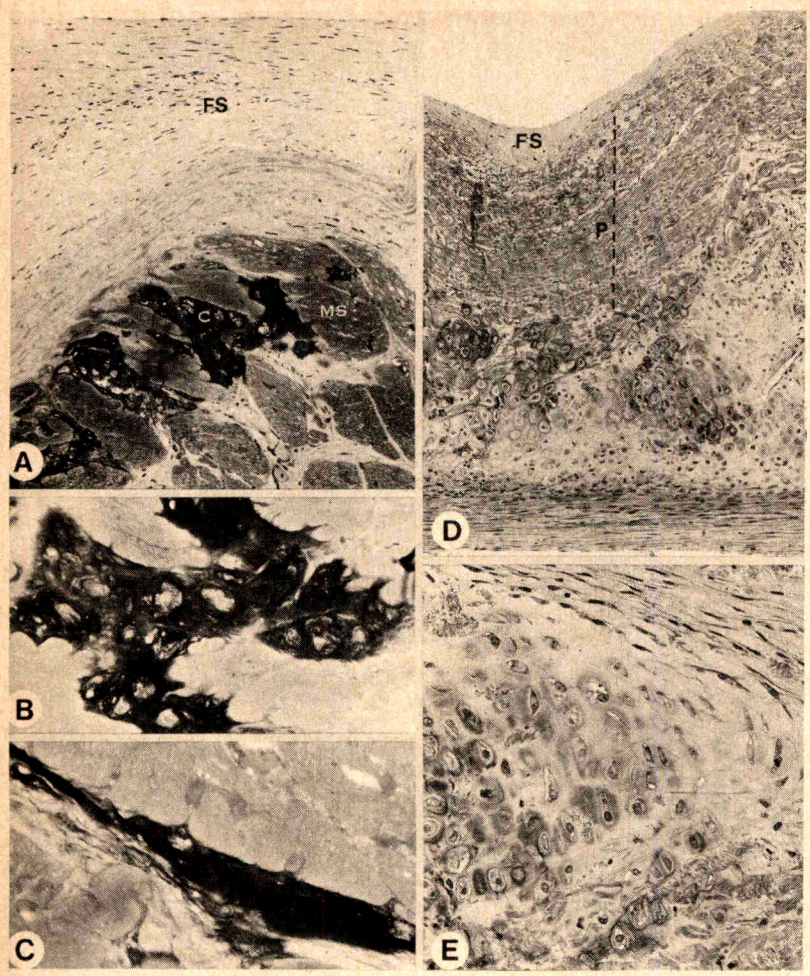

FIGURE 1. A, foci of cartilage (C) in muscle shelf (MS) of porcine aortic valvular bioprosthesis. A fibrous sheath (FS) covers the surface of the cusp. Alkaline toluidine blue stain; magnification ×100, reduced 38%. **B,** higher-magnification view of chondrocytes in area similar to that shown in **A.** The cells and their surrounding matrix have intense metachromatic staining, shown here in black. Alkaline toluidine blue stain, magnification ×250, reduced 38%. **C,** Small area of cartilage formation (**darkly stained**) in muscle shelf of another porcine aortic valvular bioprosthesis. Transversely sectioned cardiac myocytes and capillaries are immediately adjacent to the cartilage. Alkaline toluidine blue stain; magnification ×400, reduced 38%. **D,** foci of cartilage are present in fibrous sheath covering inflow surface of bovine pericardial bioprosthesis. Note the thickness of the pericardial tissue (P) and the fibrous sheaths (FS) on both surfaces of the cusps. Hematoxylin-eosin stain; magnification ×120, reduced 38%. **E,** higher-magnification view of cartilage in bovine pericardial bioprosthesis. The morphology gradually changes from elongated, fibroblast-like cells (**upper right**) to typical cartilage (**left**). Hematoxylin-eosin stain; magnification ×250, reduced 38%.

that in cartilage matrix, were recognized without any association with chondrocytes. Such areas were not considered to represent cartilage.

An area of bone and bone marrow formation (Fig. 2C and D) was observed in 1 other valve, a standard Ionescu-Shiley pericardial bioprosthesis. Although this valve did not contain cartilage, it is presumed that its bone tissue was formed by a process of calcification of cartilage.

Discussion

Hyaline cartilage is normally found in the heart of numerous species of animals,[6,7] and is usually located in the fibrous ring of the aortic valve. However, cartilage is not normally present in cardiac valves or pericardium, and it has not been described in the aortic valve of the pig or in bovine parietal pericardium, tissues used in the fabrication of the various types of commercially available bioprostheses described in the present study. Hyaline cartilage formation has been induced by ischemia in myocardial tissue,[8] by carrageenan infiltration into aortic wall,[9] by injection of formalin into conductive tissue of the atrial septum to produce heart block,[10] by implantation of devitalized skeletal and cardiac muscle into various sites[11] and by intracardiac implantation of intravenous pacemaker leads[10] and automatic defibrillator leads.[12–14] In addition, mechanical forces have been reported to induce cartilaginous transformation of fibrous connective tissue.[15]

In certain pathologic conditions, hyaline cartilage can be present in hearts and cardiac valves. Small areas of hyaline cartilage were found in the central fibrous body of the heart in 2 children who had sudden cardiac deaths.[16] Cartilaginous tissue also has been described in Mönckeberg's calcific aortic stenosis, although the characteristic pattern of alteration of the aortic valve in this disease is calcification.[17] Cartilaginous transformation of the aortic valve also was reported in a man who underwent aortic valvular replacement for aortic regurgitation of uncertain cause.[18] Foci of cartilage also have been observed in the spongiosa of the atrioventricular valves of dogs with endocardiosis,[19] and cartilage-like cells have been described in the fibrous subaortic ring of dogs with discrete subaortic stenosis.[20] In the present study, we found hyaline cartilage in 10% of 120 bioprostheses explanted from sheep ≥6 weeks after implantation. We are not aware of previous reports of cartilage in bioprosthetic cardiac valves implanted in either humans or experimental animals. In our study,

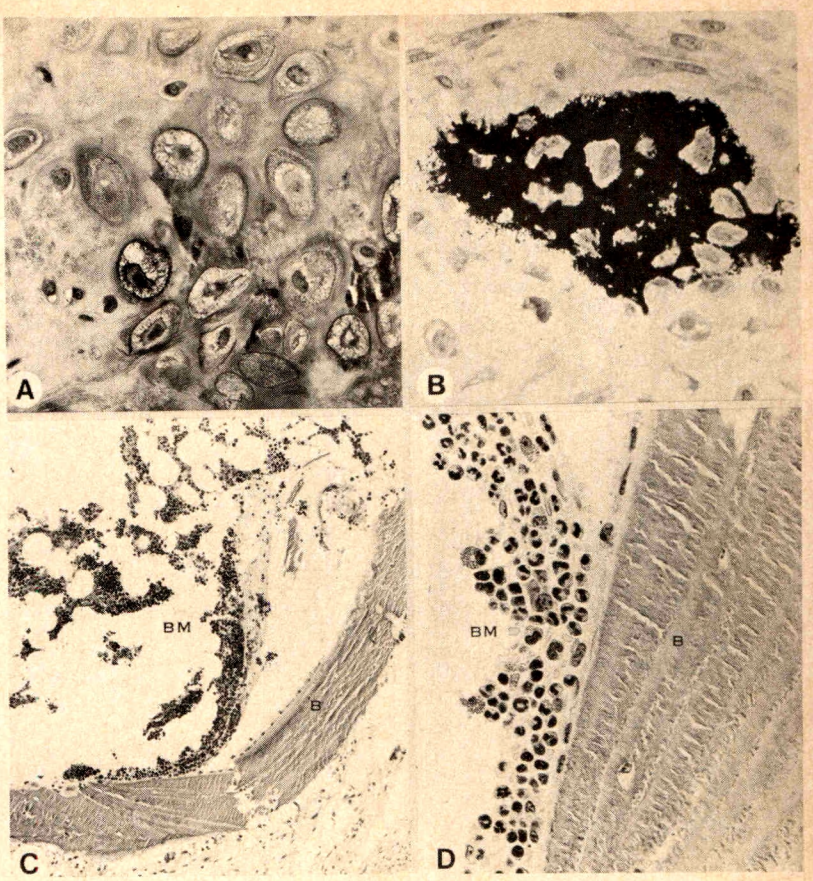

FIGURE 2. A, typical morphologic characteristics of cartilage in bovine pericardial bioprosthesis with chondrocytes lying in lacunae. Note focal calcification (**lower right**). Hematoxylin-eosin stain; magnification ×400, reduced 39%. **B,** strongly positive von Kossa reaction in area of calcification of cartilage. Fibrous sheath is shown at **top** and noncalcified cartilage at **bottom.** Hematoxylin-eosin stain; magnification ×400, reduced 39%. **C,** low- and **D,** high-magnification views of area of bone (B) and bone marrow (BM) formation in fibrous sheath (FS) of bioprosthesis. Hematoxylin-eosin stain; magnification ×100 in **C,** ×400 in **D,** reduced 39%.

the finding of cartilage could not be correlated with the extent to which calcification was present. However, cartilage was encountered more frequently in bioprostheses implanted in the tricuspid position than in those implanted in the mitral position. The reason for this difference is not known. The consistent finding of a fibrous sheath associated with cartilaginous foci and with transitional cells resembling chondrocytes in cardiac bioprosthetic valves indicates that growing and differentiating connective tissue of host origin plays a role in the cartilage formation. This observation, and the absence of cartilage in valves implanted for <6 weeks, shows that the formation of cartilage was a postimplantation event.

In their description of the mechanically induced differentiation of cartilage from fibrous connective tissue, Scapinelli and Little[15] reported that compression and rotation can cause metaplasia of typical elongated fibrous tissue cells, such as those usually found in fibrous sheaths of bioprostheses,[21] into typical rounded cartilage cells. Whether such forces are related to the formation of the cartilage observed in the present study is not known. We found that cartilage in pericardial bioprostheses usually was associated with the fibrous sheath, and that in porcine bioprostheses was associated with the muscle shelf. The formation of cartilage in the fibrous sheaths of pericardial valves would appear to be similar to that reported in the fibrous sheaths of pacing electrodes[10] and automatic defibrillator leads.[12–14] It has been postulated that devitalized cardiac or skeletal muscle contains a substance that can induce the cartilaginous transformation of primitive mesenchyme.[7,9] This seems to be the case with respect to the cartilage induced in the atrial septum by injection of formalin.[10] Thus, the devitalized cardiac muscle cells in the muscle shelf may be capable, perhaps in conjunction with mechanical forces, of inducing the formation of hyaline cartilage in porcine bioprostheses.

Hyaline cartilage is a specialized type of connective tissue composed of chondrocytes embedded in a matrix rich in proteoglycans. The microscopic appearance of hyaline cartilage in the valves in the present study differs clearly from that of fibrocartilage or elastic cartilage.[22] Chondrocytes can produce matrix vesicles, involved in the process of mineralization (endochondral calcification), which hyaline cartilage can undergo normally.[23] Our observations indicate that cartilage in bioprosthetic valves eventually calcifies, and is 1 of the several causes of mineralization of cuspal connective tissue. Only very limited morphologic observations have been reported in bioprostheses implanted in humans in the tricuspid position, the site from which most (11 of 12) of the cartilage-containing bioprostheses studied by us were explanted. Thus, it remains to be determined whether cartilage formation also occurs in bioprostheses implanted in humans.

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Syndromes of Lown-Ganong-Levine and Enhanced Atrioventricular Nodal Conduction

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Intensive investigation has led to major advances in evaluation and therapy of patients with Wolff-Parkinson-White syndrome.[1] The related syndromes of Lown-Ganong-Levine (LGL) and enhanced atrioventricular nodal conduction (EAVNC) have also been studied, but are less well understood. Moreover, LGL, a clinical and electrocardiographic syndrome, and EAVNC, an electrophysiologic syndrome, are often confused. This report examines the current understanding of these subjects.

Definitions: A short PR interval is defined, in the adult population, as a PR interval ≤0.12 second. LGL refers to the association of a short PR interval, a narrow QRS, and tachycardias, most frequently paroxysmal supraventricular tachycardia or atrial fibrillation/flutter.[2] EAVNC refers to functional criteria of atrioventricular (AV) conduction: AH interval in normal sinus rhythm ≤60 ms; 1:1 conduction through the AV node at rates up to 200 beats/min; maximal prolongation of the AH interval ≤100 ms at the fastest rate associated with 1:1 conduction.[3] Patients with LGL frequently do not have EAVNC and many patients with EAVNC do not have LGL.

Anatomic correlations: There is a paucity of data correlating structure and function in LGL and EAVNC.[4] Fibers that skirt the upper portion of the AV node and insert in the lower portion of the node have been described in normal hearts.[5] Whether these fibers assume functional significance as a partial AV node bypass in some patients is unknown. Fibers that run from atrium to His bundle, bypassing the entire AV node, were seen by Brechenmacher[6] in only 2 of 650 autopsied hearts. In 1 patient, a history of atrial fibrillation with a very rapid ventricular response suggested that this pathway had functional significance. Other hypothesized bases for EAVNC are rapidly conducting intranodal fibers, an anatomically normal but small AV node, or an anatomically normal node that exhibits enhanced function.[1]

Clinical Electrophysiology

Patients with short PR intervals: A PR interval ≤0.12 second is found in 2 to 4% of the adult population and represents the lower spectrum of a continuous unimodal distribution, not a distinct group. The short PR interval, in the absence of ventricular preexcitation, represents an AH interval that is either short or at the lower limits of normal. With atrial pacing, some patients have normal AH prolongation with development of AV Wenckebach block at the usual rates. Other patients have AV nodal delay, but in a "blunted" pattern, that is, quantitatively less delay than normal. A very small group of patients has a markedly abnormal "flat" response, with no AH increase as atrial rate is increased, and may have total bypass of the delay producing segment of the AV node.[7–9]

Although in available studies up to 60% of patients with a short PR interval have some abnormality of AV conduction, these are all selected series and the true incidence is probably much lower. Moreover, there are no data attributing any clinical significance to a short PR interval in patients without arrhythmias.

Patients with LGL: short PR interval, narrow QRS, and paroxysmal arrhythmias: Lown et al[2] described paroxysmal supraventricular tachycardia or atrial fibrillation/flutter in 17% of patients with short PR interval and narrow QRS. Ventricular tachycardia has also been described.

The incidence of EAVNC in patients with LGL has not been clearly defined. Benditt et al[10] found EAVNC in 7 of 12 patients with LGL. Given the selected nature of their study population, the true incidence is probably much lower.

Paroxysmal supraventricular tachycardia: Paroxysmal supraventricular tachycardia is the most common arrhythmia in patients with LGL. In some cases this arrhythmia represents reentry using the AV node in the anterograde direction and a concealed bypass tract in the retrograde direction. However, most often, the mechanism is reentry using a slow AV nodal pathway anterograde and a fast AV nodal pathway retrograde.[11,12]

AV nodal reentry is also the most common mechanism of paroxysmal supraventricular tachycardia in patients without LGL. Bauernfeind et al[13] found that in patients with AV nodal reentry, there was no difference in tachycardia rate between those with short and those with normal PR intervals. Although the PR interval reflects anterograde conduction over the fast AV nodal pathway, the rate during tachycardia is largely determined by anterograde conduction time over the slow AV nodal pathway. The same workers subsequently demonstrated that among patients with dual AV nodal pathways, those with a short PR interval were

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more likely to have sustained reentrant tachycardias.[14] A short PR interval implies good conduction over the fast pathway from atrium to ventricle and is associated with good conduction over the fast pathway from ventricle to atrium, an important prerequisite for sustained AV nodal reentry. Hence, LGL indicates an increased incidence of sustained AV nodal reentrant tachycardias in patients with short PR intervals.

Atrial fibrillation/flutter: The original report of Lown, Ganong and Levine[2] included 6 patients with paroxysmal atrial fibrillation and 4 with paroxysmal atrial flutter. Two of the patients with atrial fibrillation had sudden cardiac death. Atrial fibrillation and atrial flutter have particular significance in patients with LGL in the presence of EAVNC, in which rates as high as 300 beats/min have been reported.[15]

Ventricular tachycardia/ventricular fibrillation: Ventricular tachycardia has been described in patients with LGL, with and without EAVNC.[11] In patients with EAVNC, conduction of early atrial premature beats may initiate ventricular tachycardia or a very rapid ventricular response to atrial fibrillation may degenerate to ventricular fibrillation.[16,17]

EAVNC: The differentiation between EAVNC and normal AV nodal conduction is, by necessity, arbitrary. Because of the marked sensitivity of the AV node to autonomic tone, rapid conduction of the AV node is frequently seen in situations in which there is increased sympathetic tone, for example, exercise, hypotension or with the administration of sympathomimetic or anticholinergic drugs. Moreover, AV nodal conduction is age-dependent; infants and children often have 1:1 AV conduction at rates that would be abnormally fast for an adult. EAVNC may be present only with pacing from some atrial sites and not others, perhaps reflecting different AV nodal inputs.[18] Recently, EAVNC has been applied to patients who met the single criteria of 1:1 conduction at rates above 200 beats/min.[19] It should be stressed that any definition of EAVNC represents the upper spectrum of a continuous unimodal distribution of normal AV nodal function, rather than a distinct subgroup.[20]

Often there is no electrocardiographic clue to the presence of EAVNC. Benditt et al[10] found a 25% incidence of EAVNC in patients with supraventricular tachycardia and normal PR intervals. Holmes et al[21] reported 42 patients with EAVNC, defined by the single criterion of a 1:1 response at rates above 200 beats/min, and found that only 3 had short PR intervals.

EAVNC has been associated with other bypass tracts, both manifest and concealed.[3,21] In patients with accessory pathways who have paroxysmal supraventricular tachycardia, the AV node forms the anterograde limb of the reentrant circuit and the Kent bundle forms the retrograde limb. The presence of EAVNC allows rapid rates and may make management difficult.

Among patients with EAVNC, it is important to differentiate between those with blunted AH prolongation at rapid rates and those with no AH prolongation. In patients with a blunted response, concealed conduction is seen in the AV node and the ventricular response during atrial fibrillation is only moderately fast. The few patients with a flat response may have total AV nodal bypass and may have very rapid life-threatening ventricular responses to atrial fibrillation.

Pharmacology

LGL without EAVNC: Although limited information is available, these patients appear to respond to drugs like other patients with AV nodal reentry.

EAVNC: Benditt et al[22] 6 patients with EAVNC with atropine and propranolol in doses designed to induce autonomic blockade. The atrial rate at which AV Wenckebach block developed showed a marked decrease, but was still faster than in control subjects. The authors conclude that autonomic changes alone do not explain EAVNC. Nonetheless, the AV node demonstrated a definite response to autonomic blockade. Further studies are necessary.

There is a paucity of systematic information on the response of patients with EAVNC to drugs. Ideally, such information would categorize patients as to whether the AH interval showed a blunted or flat response to atrial pacing. Josephson and Kastor[12] administered propranolol to 1 patient with well-documented EAVNC and blunted response to atrial pacing. Propranolol lengthened the AH interval and caused AV Wenckebach block to appear. Benditt et al[10] studied a single patient with EAVNC with a flat AH response and found that propranolol, digoxin and quinidine had no effect on AV conduction. Kennelly and Lane[23] reported the effects of 0.75 mg of strophanthin in 3 patients with 1:1 conduction at atrial rates of 200 beats/min and blunted response of AH to increased heart rate. In 1 patient, strophanthin decreased the maximal rate at which 1:1 conduction occurred, but in the other 2 there was no effect. Moleiro et al[15] described 2 patients with EAVNC and a blunted AH response. In 1 patient, verapamil caused a marked decrease of ventricular response in atrial fibrillation. In the second patient, who had an associated short HV interval, verapamil and edrophonium had no effect on ventricular response to atrial flutter. Holmes et al[19] reported pharmacologic control in only 10 of 26 patients with EAVNC and a variety of tachyarrhythmias. Most often a Type I antiarrhythmic was used singly or in combination with digoxin or propranolol. Whether the drugs affected the *EAVNC or* had other antiarrhythmic effects is not specified. In patients with Wolff-Parkinson-White syndrome, digoxin and verapamil may increase ventricular response during atrial fibrillation. This response has not been reported in patients with EAVNC.

Hence, there are few systematic data on drug response in EAVNC. AV nodal blocking agents have a role, but are not uniformly effective. In the patient who has rapid tachycardias with debilitating symptoms, electrophysiologic testing of the effects of drugs on AV conduction should be considered.

Patients with refractory arrhythmias: For patients with EAVNC and refractory tachycardias that incorporate an accessory pathway, surgical ablation of the accessory pathway may prevent recurrent supraventricular tachycardia.[21] For patients with EAVNC with intractable rapid atrial fibrillation/flutter, direct

ablation of the His bundle with insertion of a permanent pacemaker is available as a therapy of last resort. His bundle interruption has been achieved intraoperatively using mapping localization and cryosurgical ablation[24] and, more recently, by electrical charges administered through a catheter.[25] These techniques are rarely necessary.

Conclusions: The available data allow the following conclusions. (1) A short PR interval alone is part of the normal distribution and requires no special evaluation. (2) LGL describes an association between short PR interval, narrow QRS, and tachycardias. Although patients with LGL may have a variety of arrhythmias, a short PR interval is associated with excellent retrograde fast pathway conduction in patients with dual AV pathways and, hence, greater propensity to AV nodal reentrant tachycardia. (3) EAVNC may be present in patients with normal or short PR intervals and is defined by arbitrary electrophysiologic criteria including the ability for 1:1 AV conduction at rates of 200 beats/min. EAVNC represents part of the spectrum of AV conduction, not a distinct subgroup, and does not have a clear-cut anatomic substrate. (4) EAVNC assumes clinical significance by allowing very rapid rates during supraventricular arrhythmias. (5) The response of EAVNC to medication is not well-characterized. Although AV nodal blocking agents are frequently effective, their efficacy in the individual patient cannot be predicted. (6) For the rare refractory patient, surgical and catheter ablative techniques are available.

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Torsades de Pointes Versus Polymorphous Ventricular Tachycardia

DAN TZIVONI, MD, ANDRE KEREN, MD, and SHLOMO STERN, MD

Torsade de pointes has recently gained much attention; many studies of the cause and management of this interesting and intriguing tachyarrhythmia have been published.[1–4] However, because of an unclear definition of this entity, various investigators included under the term torsades de pointes (TdP) different types of ventricular tachycardia (VT). This editorial attempts to clarify the confusion and to suggest a definition based on the unique electrophysiologic features of this arrhythmia, which requires an unorthodox therapy.

TdP was described by Dessertenne in 1966[5] as a peculiar VT with a twisting QRS axis and polymorphous appearance. The presence of QT prolongation in this form of VT was already mentioned in Dessertenne's original report, but did not receive the appropriate emphasis in this or in many subsequent studies.

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The basic underlying electrophysiologic disorder of TdP is a marked and uneven delay in myocardial repolarization, induced mainly by QT prolonging agents such as quinidine,[4] disopyramide,[6] procainamide,[7] amiodarone[8] and phenothiazines;[9] however, it may occur also with hypokalemia[10] or hypomagnesemia,[11] or even spontaneously.[12] The mechanism leading to TdP is unclear; it could be a result of either an automatic or a reentrant phenomenon.

If the definition of TdP is not strict enough and is based solely on the polymorphicity of the VT, disregarding the QT prolongation, other conditions without delayed repolarization that require completely different therapeutic approaches will also be included. Recently, Horowitz et al[3] studied 21 patients with polymorphous VT, of whom 14 had a normal QT interval; they considered the VT to be TdP. Nine of these patients were successfully treated by QT-prolonging drugs (quinidine or procainamide). Other investigators reported on the efficacy of these drugs in polymorphous VT with normal QT.[1,13] Similarly, during acute ischemia in dogs, polymorphous VT was successfully suppressed with Type I antiarrhythmic drugs when associated with normal QT intervals.[14]

Prolongation of the QT interval is the most important electrocardiographic feature differentiating TdP from polymorphous VT; this distinction has major clinical significance because it is the clue to the correct therapeutic approach. Although polymorphous VT with a normal QT can be treated with QT-prolonging drugs such as quinidine, procainamide, disopyramide and amiodarone, this type of therapy may be disastrous in TdP.[4] The successful therapy of TdP should stem logically from the underlying electrophysiologic disorder, and should therefore be aimed at shortening and possibly unifying the repolarization process. This goal can be achieved by accelerating the heart rate, either by isoproterenol or atropine or by cardiac pacing.[1,4,15,16] The simplest way to accomplish this is by isoproterenol infusion (2 to 8 μg/min), which is usually effective within a few minutes. If this drug is ineffective or is contraindicated, as in patients with acute myocardial infarction, severe angina pectoris or excessive hypertension, cardiac pacing is indicated. Because the arrhythmia is frequently associated with syncopal attacks and may be life-threatening, rapid institution of therapy is mandatory. Cardiologists and the staff of emergency rooms must be able to deliver appropriate therapy. However, if isoproterenol is given erroneously in polymorphous VT without QT prolongation, it may lead to death from intractable VT.

Serious ventricular arrhythmias arise not infrequently during antiarrhythmic therapy with quinidine, procainamide, disopyramide, and other drugs. These arrhythmias may be associated with a normal, a slightly prolonged or an excessively long QT interval. Patients with a normal QT interval, or possibly even those with slight prolongation, may respond to conventional drugs such as lidocaine or procainamide, even if the VT has a polymorphous appearance. However, when the ventricular arrhythmia is associated with a prolongation of the QT interval of $\geq$0.60 second, "true" TdP should be diagnosed[4] and the conventional therapy must be avoided. This arbitrary criterion of 0.60 second, is, we believe, the best breaking point for the diagnosis of TdP.

To prevent confusion and misdiagnosis, we propose that the diagnosis of TdP be based on the following electrocardiographic findings: (1) a prolonged QT interval ($\geq$0.60 second); (2) initiation by a ventricular premature beat with a long coupling interval; (3) twisting QRS axis of the VT; (4) repeated episodes that last for 5 to 20 beats, with spontaneous termination (unless an episode deteriorates into uniform VT or ventricular fibrillation); and (5) between episodes, multiple ventricular premature beats with ventricular couplets and triplets are commonly present.

We recommend limiting the term torsades de pointes to a VT with polymorphous appearance if this is associated with prolonged QT interval. The presence of a QT $\geq$0.60 second should call for either cessation or reduction in the dose of antiarrhythmic drugs that prolong the QT. A history of palpitation, dizziness or syncope in a patient with QT prolongation should raise the possibility of TdP, and if this entity is diagnosed, rapid institution of isoproterenol or cardiac pacing and avoidance of conventional antiarrhythmic therapy is mandatory.

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The AJC in September 1958

CAROLE A. WARNES, MB, BS, MRCP, and WILLIAM C. ROBERTS, MD

Surgical Treatment of Mitral Insufficiency (Donald B. Effler)

The September issue contained the final papers of the symposium on mitral regurgitation (MR). The symposium was dominated by surgical contributions, and demonstrates how attention at the time was focused on finding an ideal reparative operation for MR. The circumferential suture reported by Davila had gained some support, but this article described a different technique. Using a transatrial approach, 6 operations were performed with a pump oxygenator: 4 in patients with ostium primum defect and cleft mitral valve and 2 in patients with acquired MR, probably from ruptured chordae tendineae. The mitral cleft was closed by direct suture and a crescent-shaped prosthesis of pressed Ivalon, or woven Dacron®, was then placed on the atrial aspect of the repaired leaflet. The acquired MR was "repaired" by suturing the leaflets together and again covering the repair by the prosthesis (Fig. 1). Effler wrote, "The purpose of prosthesis is to take up the brunt of thrust from the ventricular contraction when the heart is restarted. It has been our fear that the valve, if repaired by suture alone, might fenestrate upon resumption of ventricular pressures." Elective cardiac arrest, still in its infancy, was used and its importance emphasized. "With the aid of cardiac arrest the heart can be lifted from its bed and rotated or displaced in any manner without the hazard of serious cardiac arrhythmia. The flaccid, arrested heart is indifferent to position or manipulation. This is of extreme importance, as it points to the obvious goal that surgeons will strive for—the replacement of a defective valve by a workable prosthetic valve."

Direct Surgical Relief of Coronary Artery Occlusion (Leonard Gottesman)

With the recognition that coronary disease often was caused by localized obstruction, the concept of operative bypass of the obstruction was considered in the late 1950s. Surgical relief of peripheral arterial obstruction had already been developed, and coronary endarterectomy had been successfully performed in humans. In this article, Gottesman described end-to-side anastomosis of the left internal mammary artery to the left circumflex coronary artery in 5 normothermic dogs under general anesthesia, using a temporary shunt for coronary blood supply (Fig. 2). Three dogs had fatal ventricular fibrillation and 2 survived, 1 of which was killed 4 weeks later and found to have a patent anastomosis. The authors concluded that such bypass techniques were feasible, and could restore blood flow distal to coronary arterial obstructions. Before the technique was applied to humans, however, they recognized that extracorporeal pump oxygenators were necessary, and the technique of coronary angiography (then performed by direct aortic puncture) would require perfection. Ten years later, aortocoronary bypass grafting was successfully performed in humans.[1]

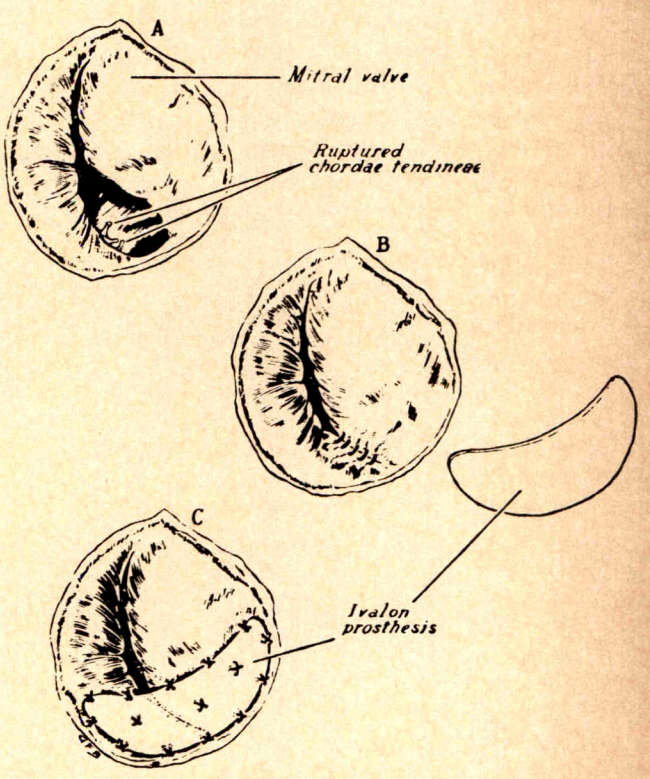

FIGURE 1. Surgical correction of mitral regurgitation performed with the pump oxygenator and elective cardiac arrest. This method is applicable to those valves with localized regurgitation. **A,** the valve with a localized "flail," secondary to ruptured chordae tendineae. **B,** direct suture to obliterate the involved commissure. **C,** reinforcement of the suture line by the crescent prosthesis.

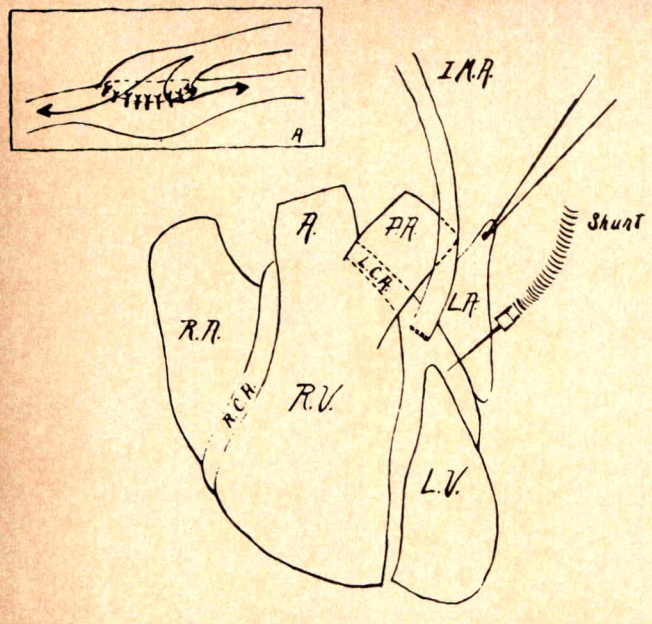

FIGURE 2. End-to-side anastomosis between internal mammary artery (IMA) and left coronary artery (LCA). Inset shows detail of end-to-side anastomosis with bidirectional flow. A = aorta; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RCA = right coronary artery; RV = right ventricle.

William Harvey Described by an Eyewitness (John Aubrey) (Saul Jarcho)

This paper consisted of excerpts from John Aubrey's "Life of William Harvey," and gave a lifelike portrayal of this founder of cardiology, complete with his foibles and virtues. The following are some excerpts.

William Harvey, was always very contemplative. . . . I remember I have heard him say he wrote a booke *De Insectis* . . . and had made dissections of Frogges, Toades, and a number of other Animals, and had made curious Observations on them. . . .

I first sawe him at Oxford, 1642, after Edgehill fight, but then was too young to be acquainted with so great a Doctor. I remember he came severall times to Trinity College to George Bathurst, B.D., who had a Hen to hatch Egges in his chamber, which they daly opened to discerne the progres and way of Generation. He was very communicative, and willing to instruct any that were modest and respectfull to him. Ah! My old Friend Dr. Harvey—I knew him right well. He made me sitt by him 2 or 3 hours together in his meditating apartment discoursing. Why, had he been stiffe, starcht, and retired, as other formall Doctors are, he had known no more than they. From the meanest person, in some way, or other, the learnedst man may learn something. Pride has been one of the greatest stoppers of the Advancement of Learning.

I have heard him say, after his Booke of the *Circulation of the Blood* came out, that he fell mightily in his Practize, and that' twas beleeved by the vulgar that he was crackbrained; and all the Physitians were against his Opinion, and envyed him; many wrote against him. With much adoe at last, in about 20 or 30 yeares time, it was received in all the Universities in the world; and, as Mr. Hobbes sayes in his book *De Corpore*, *he is the only man perhaps, that ever lived to see his owne Doctrine established in his life-time.*

All his Profession would allow him to be an excellent Anatomist, but I never heard of any that admired his Therapeutique way. I knew several practisers in London that would not have given 3d. for one of his Bills (prescriptions); and that a man could hardly tell by one of his Bills what he did aime at.

He was much and often troubled with the Gowte, and his way of Cure was thus; he would then sitt with his Legges bare, if it were a Frost, on the leads of Cockaine-house, putt them into a payle of water, till he was almost dead with cold, and betake himself to his Stove, and so 'twas gone.

He lies buried in a Vault at Hempsted in Essex, which his brother Eliab Harvey built; he is lapt in lead, and on his brest in great letters

DR. WILLIAM HARVEY

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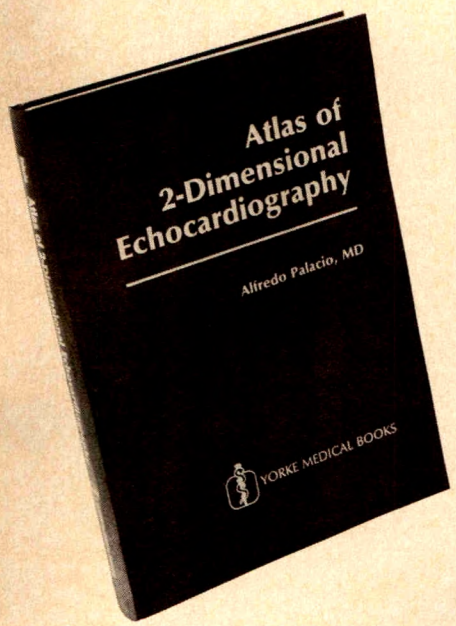

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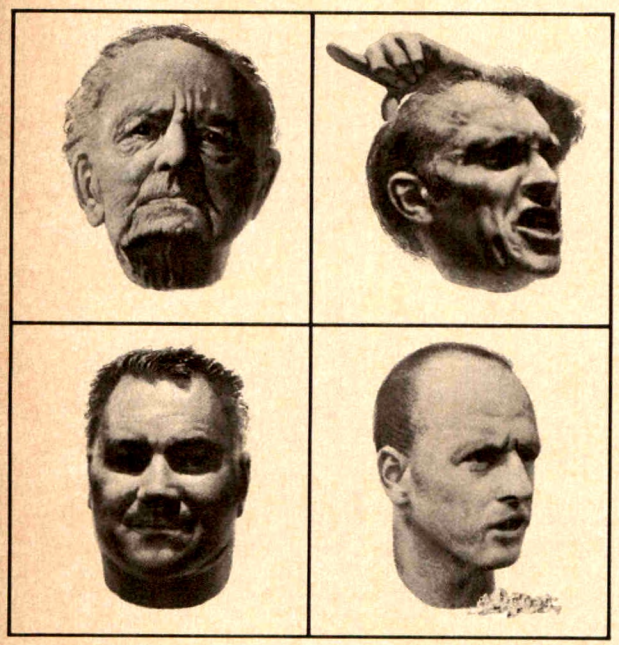

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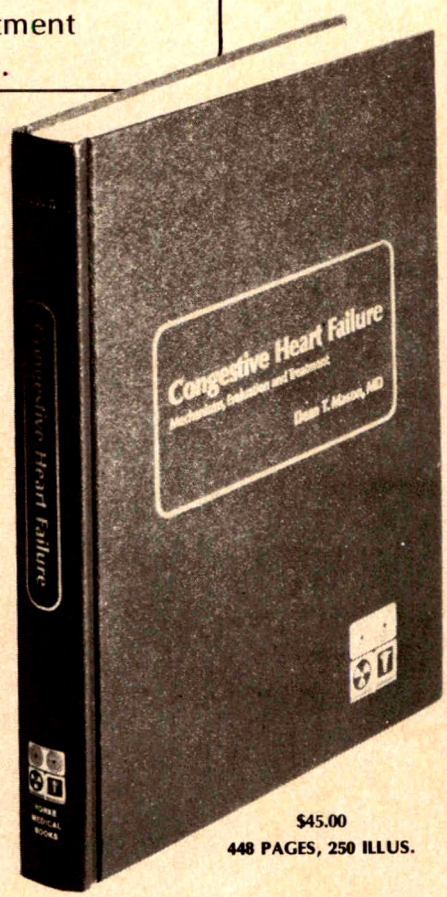

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Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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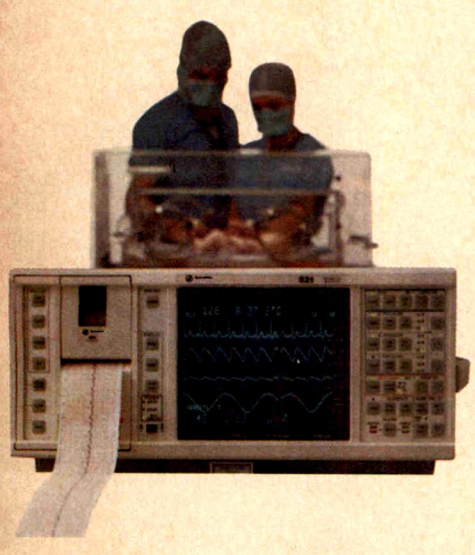

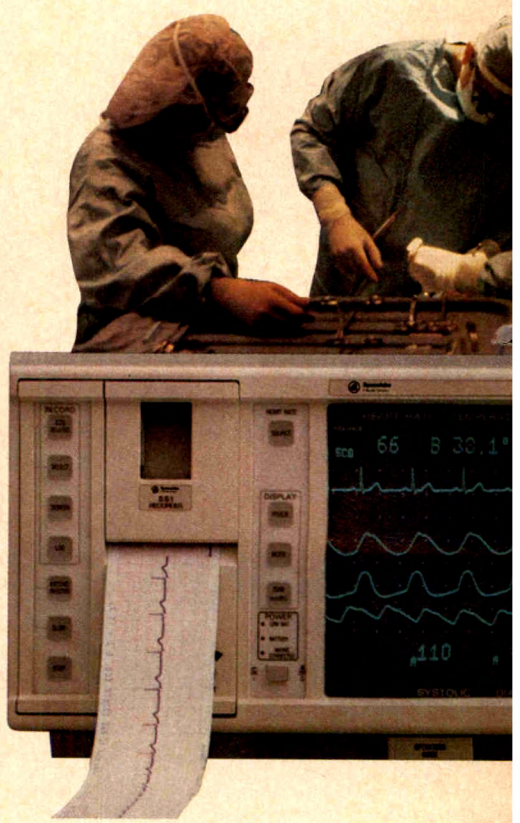

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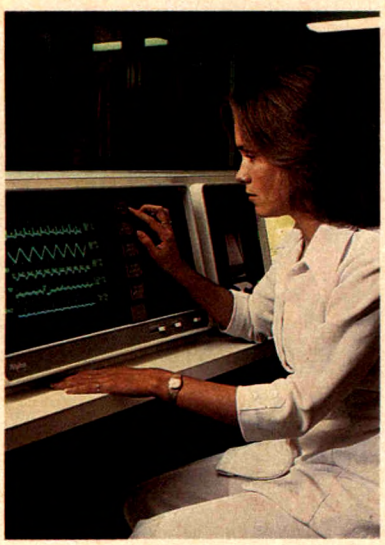

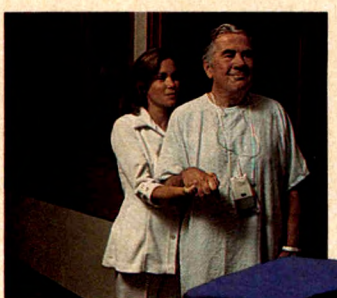

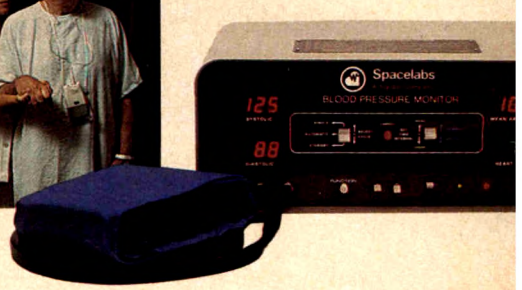

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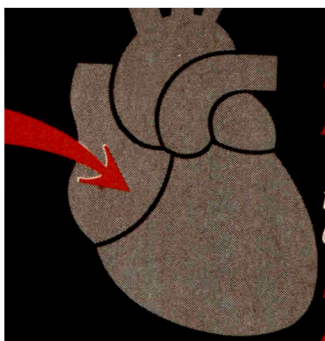

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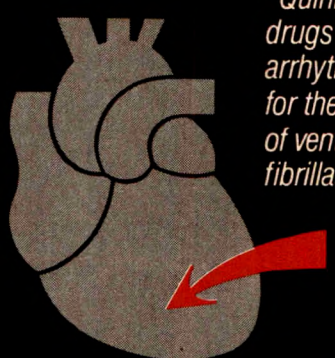

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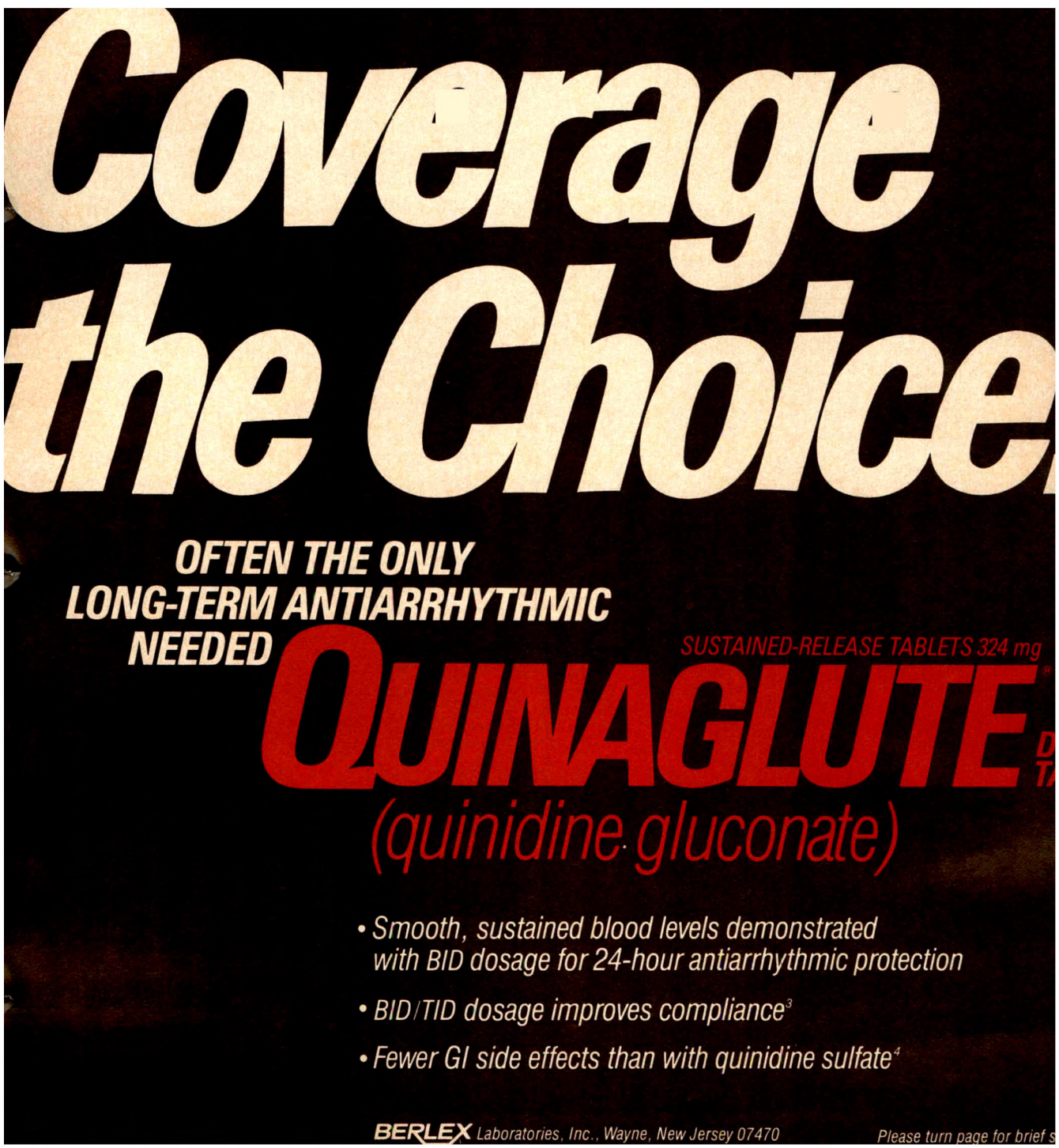
References: 1. Gettes LS: Hosp Pract 16:89-101, 1981. **2.** Bigger JT Jr, Hoffman BF: Antiarrhythmic drugs. in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 768-774. **3.** Lown B, in discussion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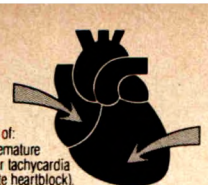

INDICATIONS AND USAGE:
Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.
2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.
3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.
4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.
5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.
7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.
8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
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NOSOCOMIAL INFECTIONS

edited by
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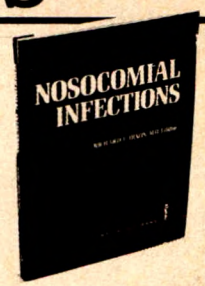

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Based on the proceedings of the 2nd International Conference on Nosocomial Infections held August 5 - 8, 1980 in Atlanta, Georgia and sponsored by the Center for Disease Control, this book provides between two covers the most comprehensive, in-depth study of this international problem published in 10 years. This major reference is divided into 11 sections consisting of 50 chapters written by over 100 internationally known experts.

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CME Test #3

Effect of Interventions in Salvaging Left Ventricular Function in Acute Myocardial Infarction: A Study of Intracoronary Streptokinase*

The University of Alabama School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marked on the instruction sheet on page A149.

1. Of 52 patients in Germany, acute thrombosis involved:
   a) the right coronary artery in 23 patients
   b) the right coronary artery in 7 patients
   c) the left coronary artery in 7 patients
   d) the left coronary artery in 4 patients

2. Of 108 patients in the University of Washington Hospital, previous myocardial infarction was present in:
   a) 32 of 62 patients with right coronary artery stenosis
   b) 21 of 46 patients with right coronary artery stenosis
   c) 21 of 46 patients with left anterior descending artery stenosis
   d) none of the above

3. In the streptokinase study there were:
   a) 2 groups: streptokinase (STK) plus coronary artery bypass grafting (CABG) and nonrevascularized
   b) 2 groups: STK and nonrevascularized
   c) 3 groups: STK plus CABG, STK, and nonrevascularized
   d) 2 groups: STK plus CABG and STK

4. In patients whose hypokinesia became worse, the decrease in motion was less in:
   a) the STK group than in the STK plus CABG group
   b) the STK plus CABG group than in the STK group
   c) the winter than in the spring
   d) males than in females

5. Hyperkinesia in acute myocardial infarction was similar in patients who did and in those who did not require:
   a) catecholamine support
   b) revascularization
   c) both STK and CABG
   d) none of the above

6. In the present study, the ejection fraction underestimated severity of hypokinesia in acute myocardial infarction and improvement of patients with optimal reperfusion because hyperkinesia:
   a) increased on the wall opposite the myocardial infarction
   b) increased on the wall of the myocardial infarction
   c) decreased on the wall of the myocardial infarction
   d) decreased on the wall opposite the myocardial infarction

7. In this study, none of the patients with rethrombosis had:
   a) ≥ 1 SD/chord improvement in hypokinesia
   b) ≥ 1 SD/chord improvement in hyperkinesia
   c) <2 SD/chord improvement in hyperkinesia
   d) <2 SD/chord improvement in hypokinesia

8. The most sensitive method for measuring hyperkinesia is the:
   a) concentrical method
   b) rectangular method
   c) radial method
   d) centerline method

9. The increase in hyperkinesia in some patients months after myocardial infarction may be due to a chronic compensation associated with:
   a) a low-sodium diet
   b) better global function
   c) maintenance of weight loss
   d) none of the above

10. Chronic hyperkinesia tended to occur more frequently in patients:
    a) with severe hypokinesia in the infarct region
    b) with severe stenosis of the artery opposite the infarct
    c) without severe stenosis of the artery opposite the infarct
    d) all the above

***This article appears on page 431 of this issue.**

A Simple Method to Interpret Cardiac and Aortic Anatomy From Chest Radiographs

T. JAMES WATERS, MD
RICHARD E. RUBIN, MD
WILLIAM C. ROBERTS, MD

In the training of cardiologists, considerable emphasis is placed on learning proper precordial examination and how to obtain and interpret electrocardiograms, echocardiograms, hemodynamics and contrast and radionuclide angiograms. In contrast, relatively little emphasis is placed on learning how to interpret "routine" radiographs of the chest. This report describes a simple technique to aid in the interpretation of the cardiac and aortic silhouette on the chest roentgenogram.

A 3 × 5 inch (7.6 ± 12.7 mm) card is cut so that it is square (3 × 3 inches) (7.6 × 7.6 mm). On the card, 4 equal-sized circles are drawn, as demonstrated in Figure 1, upper left. The circle closest to the bottom of the card represents the right ventricle (RV), the 1 to the right the right atrium (RA), the 1 toward the top the left atrium (LA) and the 1 to the left the left ventricle (LV). Between the RA and RV, of course, is the tricuspid valve (TV), and between the LA and LV is the mitral valve (MV). The aortic valve (AV) lies in the center surrounded by the circles representing each of the 4 cardiac chambers. The descending thoracic aorta (A) is located to the left of the mitral valve. The esophagus (E) is located between the LA and vertebral bodies.

After these structures are drawn on the 3 × 3 inch card, the ends of a pipe-cleaning wick are placed through the aortic valve and descending aorta and secured by bending the wire on the back of the card. The wick then represents the ascending, transverse and proximal descending thoracic aorta. The bottom of the card represents the anterior chest wall, the right (R) edge the right side of the chest, the top the posterior wall and the left (L) edge the left lateral wall of the chest. The card can now be viewed from the front (Fig. 1, upper left), left lateral position (Fig. 1, upper right), left anterior oblique (LAO) position (Fig. 1, lower left) and right anterior oblique (RAO) position (Fig. 1, lower right) simply by rotating the card.

In the left lateral (LL) position (Fig. 1, upper right) the RV is the most anterior chamber and the LA the most posteriorly located chamber. The LV and RA are midway in between. In the LAO position (Fig. 1, lower left), the RA and RV are to the left and the LA and LV to the right. This is the best view for seeing the ascending and descending thoracic aorta (Ao). In the RAO position (Fig. 1, lower right), the RA and LA form the right lateral border and the RV and LV the left lateral border. The ascending and descending thoracic aorta are superimposed.

This simple 3 × 3 inch index card with the pipe wick can be kept in the wallet or purse until these chamber locations in each of the 4 standard radiographic views are engrained. This simplified approach has made the teaching of radiographic anatomy easy.

From the Division of Cardiology, Department of Medicine, Georgetown University, and the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received and accepted May 23, 1983.

Coxsackie Viral Myocarditis Causing Transmural Right and Left Ventricular Infarction Without Coronary Narrowing

JEFFREY E. SAFFITZ, MD, PhD
DAVID J. SCHWARTZ, MD
WILLIAM SOUTHWORTH, MD
SIDNEY MURPHREE, MD
E. RENE RODRIGUEZ, MD
VICTOR J. FERRANS, MD, PhD
WILLIAM C. ROBERTS, MD

Although in adults Coxsackie viral myocarditis is usually an acute, self-limited, benign illness, it can pursue a subacute or chronic course leading to permanent cardiac dysfunction or death.[1] Such was the case in the man described here.

During 1 week, a previously healthly 38-year-old white man had progressively severe dyspnea on minimal exertion without chest pain, fever, recent flu-like syndrome, systemic hypertension, palpitations, orthopnea, paroxysmal dyspnea or heavy alcohol consumption. Examination disclosed complete heart block with a ventricular rate of 40 beats/min, Q waves in the anterior precordial leads, a markedly dilated left ventricle with segmental wall motion abnormalities (Fig. 1), and angiographically normal coronary arteries. Peripheral blood counts and thyroid function study results were normal and serologic test findings for collagen vascular diseases were negative. The erythrocyte sedimentation rate was 21 mm in 1 hour. Antibodies against Coxsackie B-1 were detected in serum at dilutions <1:10 at 1 and 4 weeks after onset of symptoms. After minimal improvement with digoxin, diuretics and permanent pacemaker implantation, symptoms of congestive heart failure (CHF) worsened, and signs of right-sided CHF became severe. The peripheral leukocyte count increased to 19,000/mm^3. Repeat serologic

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and the Departments of Pathology and Medicine, The Jewish Hospital of St. Louis and Washington University School of Medicine, St. Louis, Missouri. Manuscript received and accepted June 3, 1983.

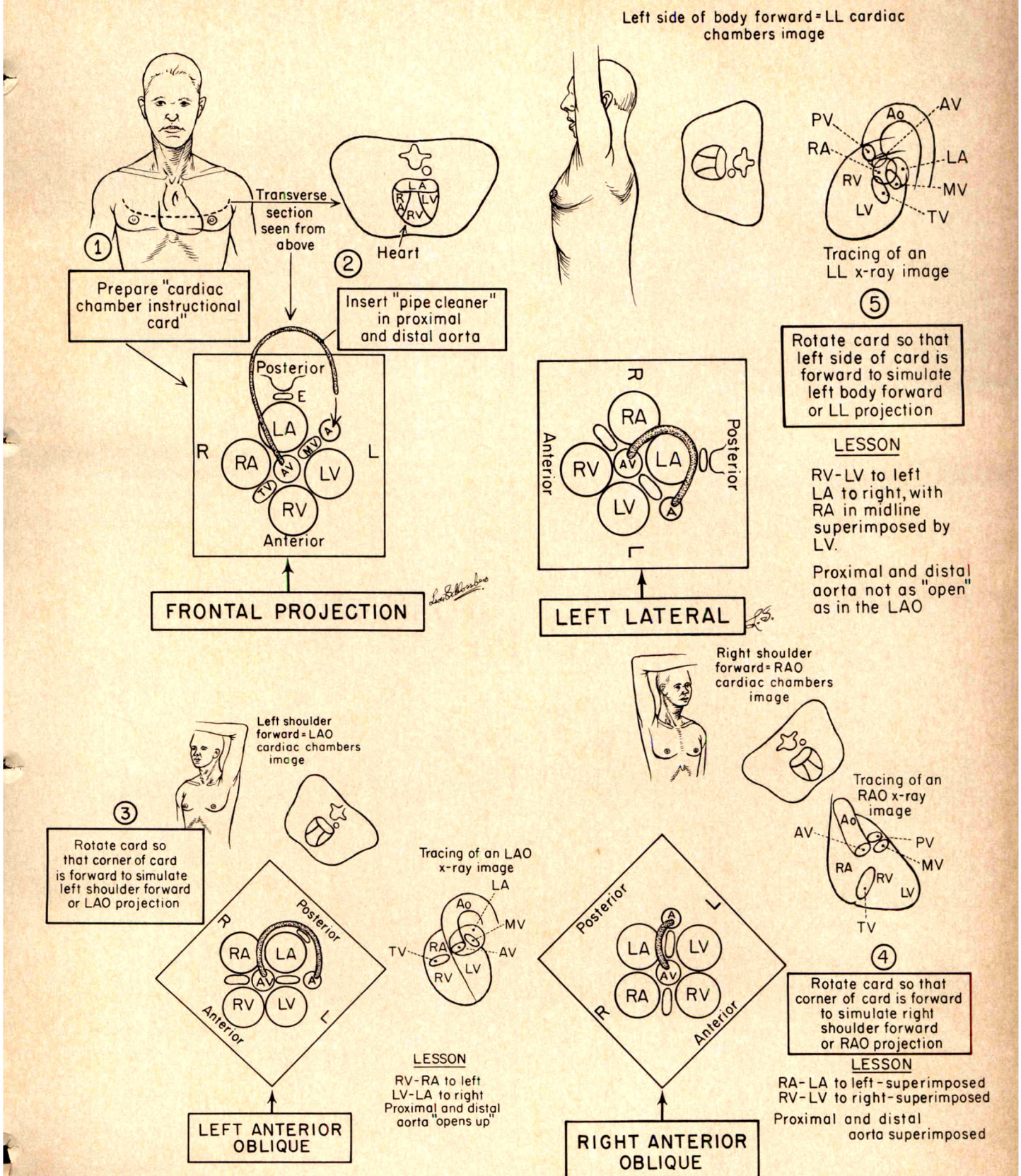

FIGURE 1. Technique described in the text for interpreting the cardiac and aortic silhouette on the chest roentgenogram. PV = pulmonic valve; other abbreviations are as defined in the text.

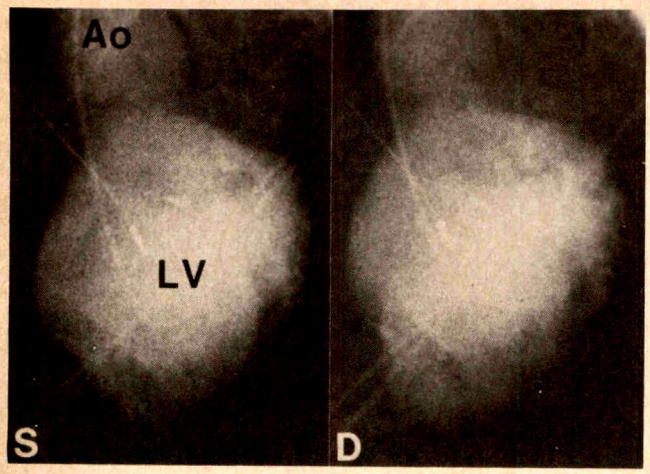

FIGURE 1. Left ventriculogram (cranial left anterior oblique projection) showing end-systolic (S) and end-diastolic (D) ventricular configurations. There are segmental wall motion abnormalities with less severe hypokinesia of the apical and proximal septal segments. Ao = aorta; LV = left ventricle.

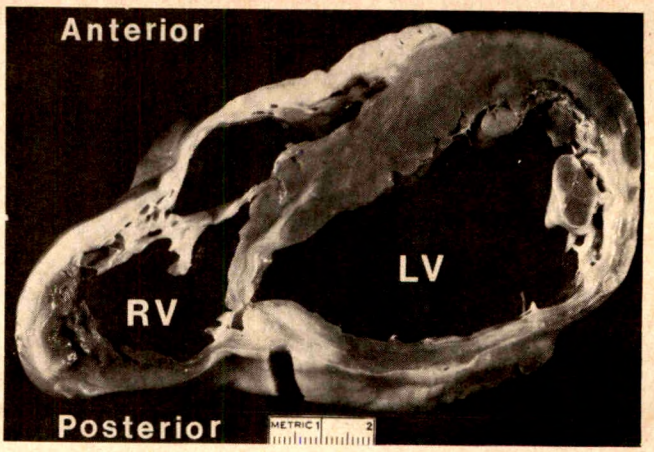

FIGURE 2. Portion of cardiac ventricles cut transversely showing markedly dilated right and left ventricles (RV and LV). Much of the anterolateral wall of the RV and posteroseptal and lateral walls of LV are replaced by scar tissue.

studies 4 months after onset of symptoms disclosed a >12-fold increase in antibodies against Coxsackie B-1 (>1:128) without increases in other viral antibodies. The patient died 4.5 months after the onset of symptoms from severe CHF.

At necropsy (The Jewish Hospital of St. Louis, #A82-83), the heart weighed 470 g. Both ventricular chambers were markedly dilated (Fig. 2). Much of the anterolateral wall of the right ventricle, the posterolateral wall of the left ventricle and the posterior portion of the ventricular septum was replaced by fibrous tissue (Fig. 2). The coronary arteries were insignificantly (<25% cross-sectional area) narrowed. Histologic examination discosed extensive lymphocytic infiltrates, fibrous tissue and necrotic and degenerated myocytes (Fig. 3). Ultrastructural examination of myocardium did not disclose Coxsackie viral particles.

Coxsackie B-1 myocarditis, documented by serologic tests, had an unusually virulent course, causing profound CHF and widespread myocardial destruction in our patient. The noncardiac organs and tissues, including skeletal muscle, were not involved by the inflammatory process. An unusual feature was extensive transmural scarring of the walls of both ventricles, which resulted in segmental wall motion abnormalities. Studies in experimental models have documented CHF as a complication of viral myocarditis[2] and suggest a role of viruses in the pathogenesis of idiopathic dilated cardiomyopathy. Transmural right and left ventricular

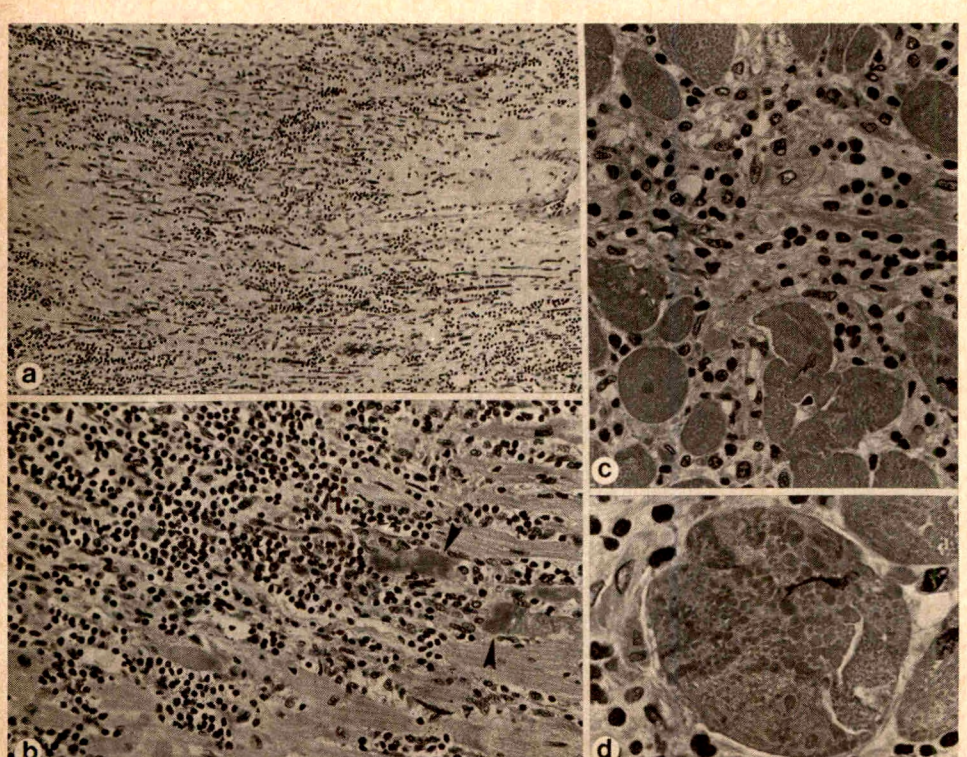

FIGURE 3. Photomicrographs of portions of left ventricle. **a,** area of left ventricular free wall showing extensive lymphocytic infiltrate and replacement of the myocytes by fibrous connective tissue. **b,** higher magnification view of border zone between viable myocardium (right) and scar tissue (left) showing numerous lymphocytes and focally necrotic myocytes (**arrowheads**). **c,** 1-μm-thick sections of left ventricular free wall showing an area of interstitial fibrosis, myocytic hypertrophy, and lymphocytic infiltrates. The myocytes vary in diameter. **d,** Large, hypertrophied, degenerating myocyte showing loss of myofibrils. All sections stained with hematoxylin-eosin; magnification ×120 (a), ×200 (b), ×300 (c), ×700 (d); reduced 42%.

scarring is rare in patients with idiopathic dilated cardiomyopathy. In 1 reported patient, a 62-year-old woman with symptoms of cardiac dysfunction from dilated cardiomyopathy for 9 years, necropsy disclosed cardiac findings nearly identical to those in the patient described herein, except that inflammatory cells were absent in the scarred myocardium.[3]

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Active Infective Endocarditis Complicating Idiopathic Dilated Cardiomyopathy

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The occurrence of infective endocarditis in patients with habitual alcoholism is fairly frequent.[1] A high percentage of patients with idiopathic dilated cardiomyopathy are habitual alcoholics. Yet, the occurrence of infective endocarditis in patients with idiopathic dilated cardiomyopathy is extremely rare. Such was the case, however, in the patient described here.

AW, a 60-year-old man, had been a habitual alcoholic for many years and had the onset of chronic congestive heart failure (CHF) at age 53 years. About 1 year before death, periodic ventricular tachycardia with syncope occurred and he had 2 episodes of ventricular fibrillation with successful resuscitation. The ejection fraction was 19%. His final hospitalization was precipitated by worsening CHF. The blood pressure was 100/80 mm Hg and the temperature 37°C. A grade 3/6 systolic blowing murmur was heard over the cardiac apex. Four of 4 blood cultures grew Staphylococcus aureus *and a chest radiograph showed an infiltrate consistent with acute pneumonia in each lung. Death was attributed to progressive CHF and pneumonia.*

At necropsy, the heart weighed 595 g. The coronary arteries were virtually devoid of atherosclerotic plaques. A thrombus was present in the right atrial appendage. All 4 cardiac chambers were dilated, particularly the ventricles. Several mural endocardial white plaques were present in the left ventricle. A vegetation that measured about 1 cm in maximal diameter and consisted of colonies of Gram-positive organisms, pus and fibrin was present on the atrial aspect of the posterior mitral leaflet (Fig. 1 and 2). The underlying leaflets and chordae tendineae were normal.

Of 165 patients with idiopathic dilated cardiomyopathy studied at necropsy in the Pathology Branch of the National Heart, Lung, and Blood Institute, the patient described in this report is the only 1 with evidence of either active or healed infective endocarditis; we are not aware of any published reports that mention infective endocarditis complicating idiopathic dilated cardiomyopathy. The endocarditis in our patient was probably a consequence of the acute pneumonia, since similar colonies of organisms were present in both the lung and the mitral vegetation.

It has been recognized for decades that active infective endocarditis is a rare occurrence in patients with chronic CHF. Our patient is an exception and illustrates that on rare occasion, a patient with extremely diminished cardiac output can still develop infective endocarditis, even on a previously anatomically normal valve. The endocarditis in our patient was probably secondary to the acute pneumonia. Had the pneumonia not been present, the infective endocarditis likely would not have occurred.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received and accepted June 3, 1983.

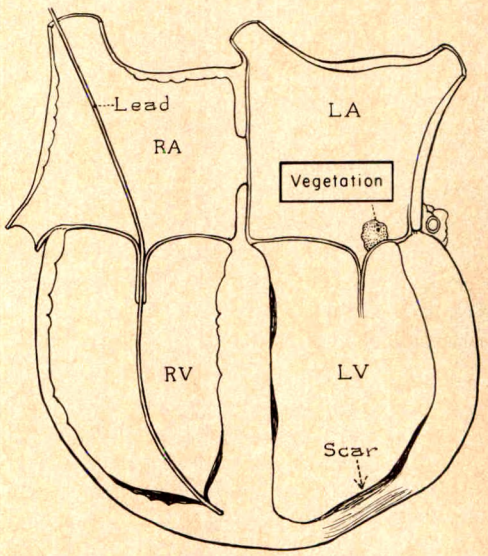

FIGURE 1. Drawing of vegetation on the atrial side of the posterior mitral leaflet. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

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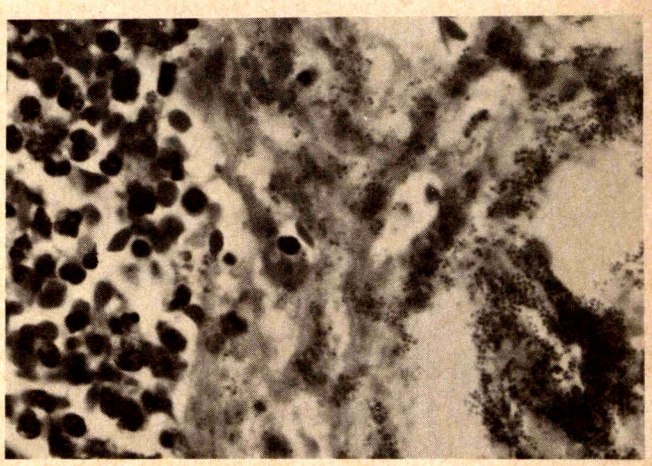

FIGURE 2. Photomicrograph of a section of a portion of the mitral valve vegetation showing colonies of Gram-positive organisms and a collection of polymorphonuclear leukocytes. Hematoxylin-eosin stain; magnification ×860, reduced 13%.

Acute Pulmonary Edema Induced by Left Bundle Branch Block

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The hemodynamic effects of altered electrical activation and the subsequent altered mechanical contraction during left bundle branch block (LBBB) in man and experimental preparations are controversial.[1–5] The apparently different reported hemodynamic effects of LBBB may, in part, be due to different underlying cardiac diseases. At issue is whether abnormal activation sequence can result in depressed ventricular function. Acute pulmonary edema caused by LBBB has not previously been described, but did occur in a patient with dilated cardiomyopathy and normal coronary arteries. This patient is described in this report.

A 54-year-old man first had cardiomegaly at age 19 years, first noticed exertional dyspnea at age 45 and severe dyspnea, orthopnea, and paroxysmal nocturnal dyspnea at age 49. Cardiac catheterization (Table I) demonstrated marked left ventricular (LV) dilation, an ejection fraction of 21%, no mitral regurgitation, and normal coronary arteries. Increased dyspnea despite digoxin, furosemide, procainamide, amrinone, prazosin, and potassium chloride led to hospitalization.

Blood pressure was 92/64 mm Hg, heart rate 74 beats/min, and respirations 26 breaths/min. Jugular venous pressure was abnormally increased, and the a wave was dominant. Bilateral basilar rales were present. LV apical impulse was diffuse with presystolic expansion. S_1 and S_2 were normal. A grade 1/6 holosystolic murmur was heard at the apex. Atrial and ventricular diastolic gallops were present. Neither hepatomegaly nor subcutaneous edema was present.

The chest radiograph demonstrated cardiomegaly and pulmonary venous hypertension. The electrocardiogram (Fig. 1) showed sinus rhythm, left atrial enlargement, ST-T abnormalities, and a nonspecific intraventricular conduction delay (IVCD, QRS width 0.11 second).

The patient had 3 episodes of acute pulmonary edema, all associated with the onset of LBBB (QRS width 0.15 second). A premature atrial contraction initiated LBBB at a faster heart rate (Fig. 2). In 15 minutes, the patient was acutely dyspneic, the holosystolic murmur increased 1 grade in intensity, and a large V wave was seen in the pulmonary artery wedge pressure (Table I). The electrocardiogram reverted to the IVCD and the pulmonary edema resolved. He was taken to the catheterization laboratory, where baseline data were obtained at a heart rate of 80 beats/min (Fig. 3, top). Brief atrial pacing at a rate of 102 beats/min initiated LBBB; when atrial pacing was stopped, LBBB persisted at a rate of 84 beats/min. Repeat hemodynamic measurements were obtained after 3 minutes. Transient sinus slowing produced by carotid sinus massage resulted in reversion to IVCD. Recovery hemodynamic measurements were obtained after 3 minutes. Accompanying the LBBB, the mean pulmonary artery wedge pressure and V wave increased (Fig. 3, middle), as did the pulmonary artery pressure, pulmonary vascular resistance, and arteriovenous oxygen difference (Table I). Cardiac output did not change and the systemic arterial pressure decreased slightly. These values returned toward baseline values after reversion of the electrocardiogram to the IVCD (Table I, Fig. 3, bottom).

TABLE I Cardiac Catheterization Data

		1982			
	1978	5/15 LBBB	5/27 Baseline	5/27 LBBB	5/27 Recovery
RA (mm Hg)					
A	9	...	5	...	...
V	8	...	4	...	...
Mean	7	12	4	...	...
RV (mm Hg)	29/8	70/13	33/8	...	...
PA (mm Hg)	25/17	70/45	33/23	44/26	33/24
Mean	21	52	26	36	27
PAW (mm Hg)					
A	11	...	18	26	18
V	11	52	24	33	23
Mean	9	37	20	28	18
LBA (mm Hg)	113/70	110/60	99/61	91/59	105/65
Mean	85	77	72	70	75
CO* (liters/min)	5.36* (Fick)	5.1	3.5	3.8	3.7
AVO_2 (vol %)	5.5	11.1	5.8	6.4	6.1
PVR (Wood units)	2.8	2.9	1.7	2.1	2.4
HR (beats/min)	67†	100	80	84	82

* Cardiac output in 1982 was determined by the thermodilution method.
† Heart rate during angiography.
AVO_2 = arteriovenous oxygen difference; HR = heart rate; LBA = left brachial artery; LBBB = left bundle branch block; LV = left ventricle; PA = pulmonary artery; PAW = pulmonary artery wedge; PVR = pulmonary vascular resistance; RA = right atrium; RV = right ventricle.

In this patient, rate-related LBBB (that is, altered LV activation) was shown clearly by a sequential study to result in pulmonary edema. Two possible causes of the pulmonary edema are decreased cardiac performance and increased mitral regurgitation. Impaired LV hemodynamic function was likely produced because the mean filling pressure increased from 20 to 28 mm Hg at a lower LV systolic pressure and with little change in the forward stroke volume, suggesting that this ventricle was operating on a depressed function curve during LBBB. Haft et al[6] studied 24 patients with LBBB (7 with coronary artery disease, 5 with cardiomyopathy, and 7 with valvular disease) and found that only patients with coronary artery disease had abnormal LV contraction. Williams et al[7] studied 12 patients with LBBB without significant coronary disease; using biplane cineangiograms and quantitative analysis, 10 had wall motion abnormalities.

An additional likely cause of the acute increase in mean pulmonary arterial wedge pressure and in the development of a large V wave is the development of

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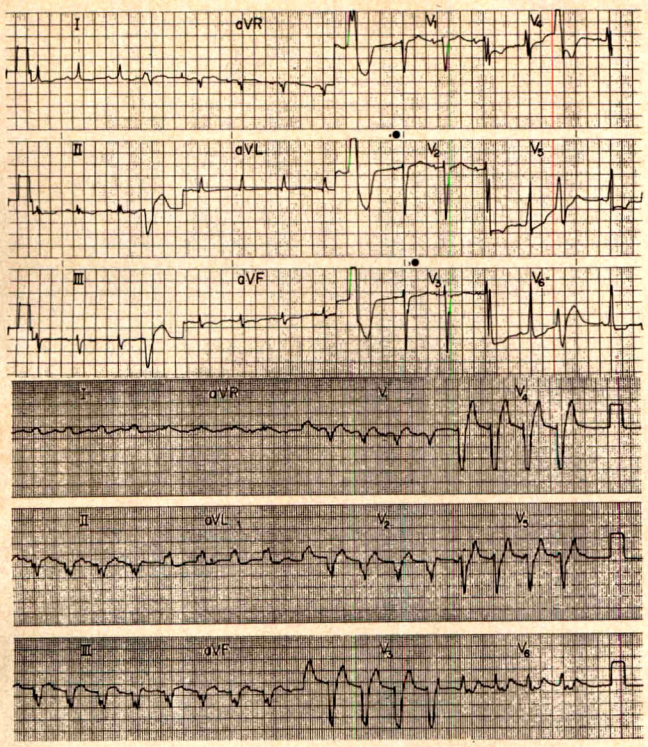

FIGURE 1. Top 3 recordings, baseline electrocardiogram showing sinus rhythm, left atrial enlargement and an intraventricular conduction delay (QRS width, 0.11 second). The rate is 82 beats/min. **Bottom 3 recordings,** electrocardiogram taken during an episode of acute pulmonary edema showing left-axis deviation and complete left bundle branch block (QRS width, 0.15 second). The rate is 102 beats/min.

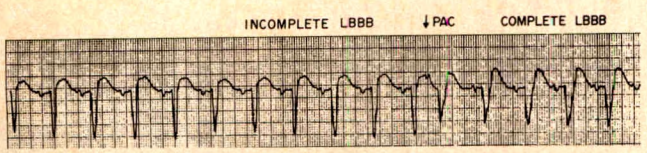

FIGURE 2. Rhythm strip from the intensive care unit showing initiation of left bundle branch block (LBBB) by a premature atrial contraction (PAC).

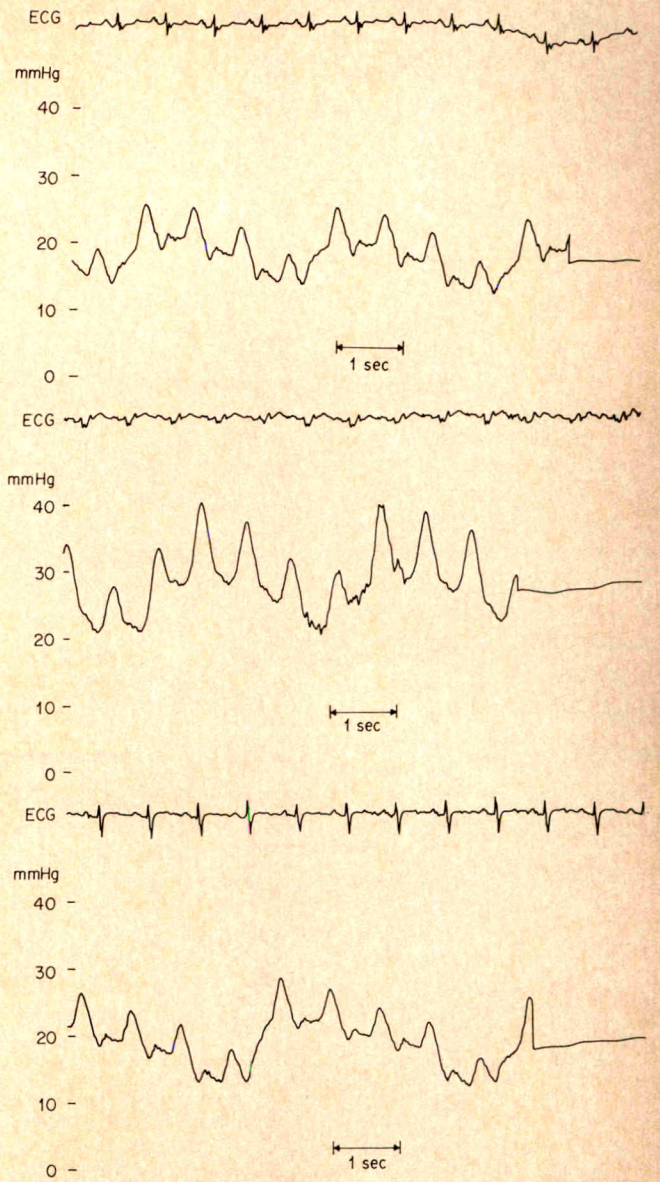

FIGURE 3. Pulmonary artery wedge tracings: baseline (**top**); left bundle branch block (**middle**), and recovery (**bottom**). ECG = electrocardiogram.

increased mitral regurgitation with the onset of LBBB. Increased mitral regurgitation during LBBB may be caused by either an alteration in the timing of contraction of the papillary muscles or an alteration in the shape of the mitral valve anulus or both. The latter explanation would imply that the regurgitation may have followed LV enlargement due to depressed function. Alteration in the timing of contraction of the papillary muscles and adjacent LV myocardium as occurs in LBBB might further distort the mitral valve anulus to cause increased mitral regurgitation. The results in our patient suggest that abnormal ventricular activation can result in clinically significant LV dysfunction, at least in patients with abnormal LV myocardium.

Acknowledgment: We thank John Ross, Jr., M.D., and Ralph Shabetai, M.D., for their help. Kurt Smolen prepared the illustrations and Tammy Shaffer typed the manuscript.

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Diagnosis of Left Ventricular to Right Atrial Shunt Utilizing Contrast Echocardiography

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A left ventricular (LV)-to-right atrial (RA) shunt is an uncommon condition that usually results from a congenital defect.[1] Rarely, such lesions may be acquired after infective endocarditis,[2] valve replacement[3] or trauma.[4] We describe a case in which a LV–RA fistula occurred after aortic valve replacement. The echocardiographic findings were diagnostic.

A 23-year-old man, an intravenous drug abuser, developed severe aortic regurgitation (AR) with stroke from Staphylococcus aureus *endocarditis. Twelve days after the initial onset of symptoms, heart surgery was performed and confirmed the clinical, echocardiographic and angiographic findings of a ring abscess involving the aortic valve noncoronary cusp and severe destruction of the aortic valve cusps and septal leaflet of the triscupid valve. Debridement of the abscess cavity, excision of the septal leaflet of the tricuspid valve, and aortic valve replacement with a 23-mm Ionescu-Shiley prosthetic valve was performed. On the 29th postoperative day, a new diastolic murmur was heard, which was loudest at the upper right sternal border. The hemodynamics were stable and blood cultures were negative; the patient was discharged 2 months after surgery.*

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During the next 10 months the appearance of ascites, peripheral edema and jaundice necessitated readmission. Examination revealed a grade 3/6 systolic murmur, a grade 3/6 diastolic murmur best heard at the lower left sternal border, and findings compatible with moderately severe tricuspid regurgitation. Aortic root angiography revealed mild AR and an aneurysm of the sinus of Valsalva. Left ventriculography demonstrated a ventricular septal defect; however, visualization of the right-sided chamber was inadequate to determine if the shunt entered the right atrium or right ventricle. Blood samples for oxygen saturation were obtained from the pulmonary artery, right atrium and left ventricle and were compatible with a 2:1 left-to-right shunt, but because of severe tricuspid regurgitation the exact level of the shunt could not be determined. However, 2-dimensional saline contrast echocardiography performed later revealed the defect and accurately delineated the chambers involved (Fig. 1). At operation, the echocardiographic finding of the LV-RA fistula was confirmed. The defect was approximately 1.5 cm in diameter and was closed with pledget sutures. The tricuspid valve was replaced with a porcine heterograft prosthesis. Postoperatively, ascites, jaundice, peripheral edema and hepatomegaly resolved completely.

The unique feature of this case was the use of 2-dimensional echocardiography, which allowed us to visualize the defect and accurately predict its anatomic location. Because the size of acquired LV-RA fistula has generally been >0.4 cm, echocardiographic visualization of these fistulas would appear feasible. In our patient, the identification of the defect was best accomplished in the short-axis view at a level just below the aortic valve; the defect also was seen in the apical long-axis view, but with far less clarity.

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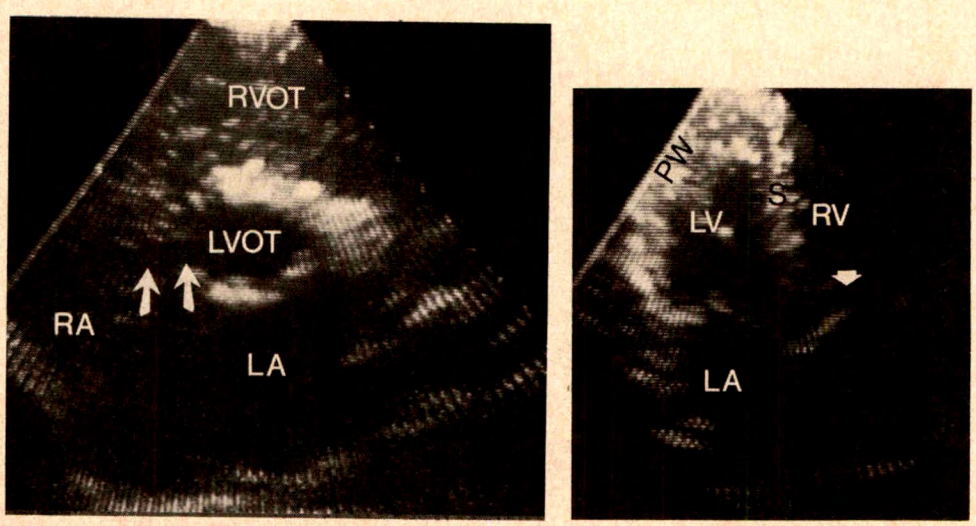

FIGURE 1. Parasternal short- **(left)** and modified apical long-axis **(right)** views. **Left,** with the transducer angled just below the aortic valve, the communication between the right atrium (RA) and left ventricular outflow tract (LVOT) is seen. A negative contrast **(arrows)** documents a left-to-right shunt. Note the enlarged left atrium (LA) and right ventricular outflow tract (RVOT). **Right,** the defect **(arrow)** is seen. LV = left ventricle; PW = posterior wall; RV = right ventricle; S = septum.

Thrombocytosis and Fatal Coronary Heart Disease

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Although thrombocytosis may cause vascular thrombosis with resultant organ or tissue ischemia, the occurrence of coronary thrombosis and myocardial infarction (MI) in this circumstance is rare. To our knowledge, this association has been reported only once previously, in a 22-year-old man.[1] In this report, we describe another 22-year-old man with fatal congestive heart failure almost a year after a large MI associated with thrombocytosis.

A 22-year-old man developed intermittent hematuria at age 5 years and systemic hypertension and proteinuria at age 7 years. Although the hypertension and proteinuria persisted, extensive evaluation at age 19 years, including renal biopsy, disclosed no specific abnormalities. The platelet count at that time was 231,000/mm^3. At age 21 years, sudden, severe precordial pain appeared and an acute anterior wall MI was documented. The platelet count ranged from 400,000 to 600,000/mm^3. The MI was complicated by ventricular arrhythmias and thromboemboli, which required embolectomy in both legs. A month after onset of the acute MI, congestive heart failure (CHF) prompted catheterization, which disclosed total occlusion of the right and left anterior descending coronary arteries (R and LAD) and an apical left ventricular (LV) aneurysm. The total serum cholesterol level was 174 mg/dl. Sudden pain, cyanosis and coolness of the left index finger occurred 6 months after the acute MI. At that time, he underwent embolectomy of the left brachial and radial arteries and the LV aneurysm in the anterior wall was excised. The aneurysm contained thrombus. CHF persisted and he was hospitalized several times. The platelet counts

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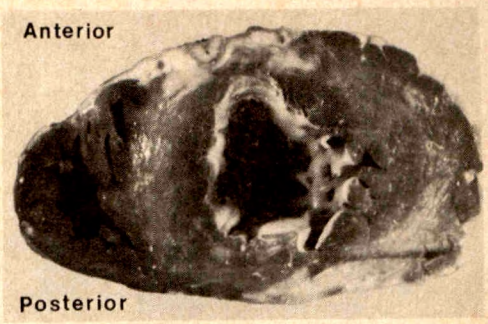

FIGURE 1. A transverse section of the heart at necropsy showing healed infarcts in the anterior and posterior left ventricular walls and fresh mural thrombus overlying dense white endocardial fibrous tissue.

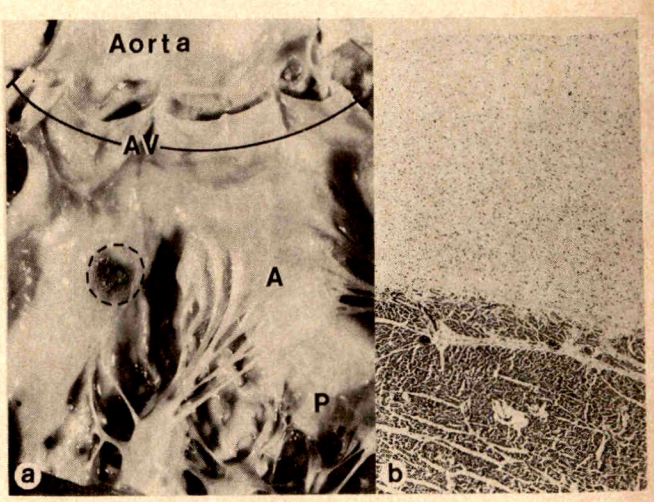

FIGURE 2. a, Opened left ventricle, aortic valve (AV) and aorta showing markedly thickened endocardial fibrous tissue overlying scarred myocardium. Enclosed in the dashed circle is a small thrombus. A and P = anterior and posterior mitral leaflets. **b,** Photomicrograph showing fibrous tissue overlying mural endocardium. The connective tissue is similar to that in the lumen of the occluded epicardial coronary arteries. Hematoxylin-eosin stain; magnification ×54, reduced 44%.

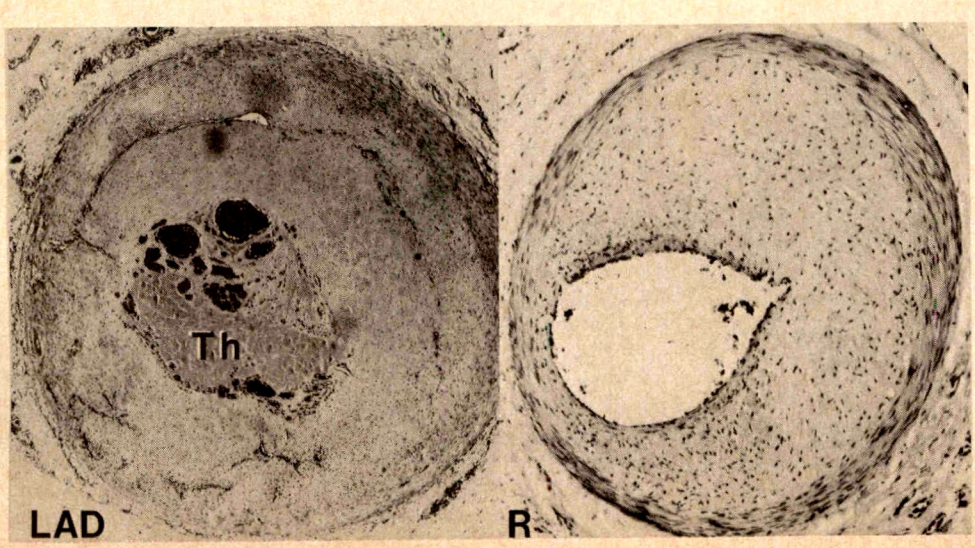

FIGURE 3. Photomicrographs of a cross section of the left anterior descending coronary artery (LAD) and a branch of the right coronary artery (R). The LAD is severely narrowed by fibrocellular tissue. Multiple channels and fresh platelet-fibrin thrombus (Th) are present. The branch of the right coronary artery is narrowed by connective tissue, similar to that shown in Figure 1. Neither vessel contains foam cells, cholesterol clefts, calcific deposits or pultaceous debris. Hematoxylin-eosin stains; magnification ×38 (LAD), ×107 (R); reduced 25%.

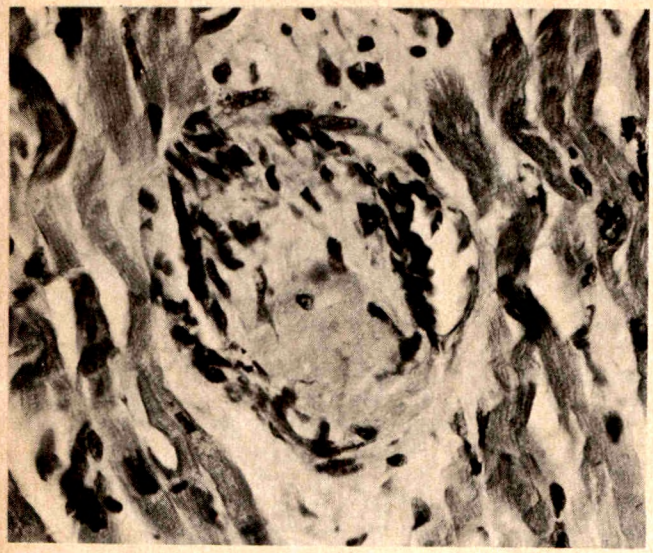

FIGURE 4. Photomicrograph of portion of left ventricular myocardium showing small intramural coronary artery containing platelet-fibrin thromboemboli. Hematoxylin-eosin stain; magnification ×430, reduced 13%.

ranged from 400,000 to 800,000/mm³. The final hospital admission at age 22 years was necessitated by severe CHF and ischemia of the distal left fourth finger. Cardiac output and blood pressure diminished progressively and the patient died 10.5 months after the acute MI.

At necropsy (Medical College of Ohio #A-82-2), the heart weighed 450 g. The apical half of the anterior LV free wall was replaced by dense scar at and adjacent to the LV aneurysectomy incision (Fig. 1). The posterior LV wall was also scarred. The LV apex contained mural thrombus adherent to underlying endocardial fibrous tissue. Fresh and organized mural thrombus also covered the LV outflow tract (Fig. 2). The R and LAD were totally occluded proximally; the length of the LAD occlusion was approximately 2 cm and that of the R 4 cm. The other portions of the LAD and R and the entire left circumflex artery were normal. Branches of the major epicardial coronary contained discrete focal severe narrowings with normal intervening areas. Histologic examination of the narrowed coronary arterial segments showed fibrocellular intimal profileration without foam cells, cholesterol clefts, pultaceous debris or calcific deposits (Fig. 3). In some segments, the lumen contained several small channels, and a platelet-fibrin thrombus was present in the LAD (Fig. 3). The intima of the narrowed coronary arteries was similar histologically to the thickened fibrous tissue on the LV mural endocardium (Fig. 4). Histologic examination of LV myocardium disclosed necrosis adjacent to the healed MI and multiple small intramural coronary vessels with platelet-fibrin thromboemboli (Fig. 4). Both the spleen and lung contained discrete infarcts. The aorta was free of atherosclerotic plaques. The bone marrow, specifically the megakaryocytes, was normal. The kidneys contained focal hyaline sclerosis of glomerular capillary tufts consistent with organized microthrombi, but no other abnormalities to explain the hematuria and proteinuria throughout childhood. (Sections of kidney were examined by John M. Kissane, MD, a recognized renal expert, who agreed with our renal diagnosis.)

Thrombocytosis appears to be the only reasonable cause of the fatal coronary artery disease in the patient described here. The presence of thromboemboli in the intramural coronary arteries, in peripheral, splenic, pulmonary and renal arteries, the young age of the patient, the morphologic features of the luminal material that caused the multiple arterial narrowings (that is, its dissimilarity to atherosclerotic plaques) all strongly support the view that the arterial narrowings in this patient were the result of thrombocytosis.

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Left Ventricular Outflow Obstruction Caused by a Starr-Edwards Mitral Prosthesis

PETER C. D. PELIKAN, MD
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NICHOLAS J. FORTUIN, MD
FRANK C. P. YIN, PhD, MD

The Starr-Edwards caged-ball prosthesis is the most bulky prosthesis and might be expected to have unique complications, especially when used in the mitral position in a small ventricle. This report documents left ventricular (LV) outflow tract obstruction caused by a Starr-Edwards prosthesis in the mitral valve (MV) position.

From the Cardiology Division, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland. Manuscript received April 22, 1983; revision received May 13, 1983, accepted May 17, 1983.

N.H. was evaluated in 1972, when she was 61 years old, because of progressive dyspnea on exertion and atrial fibrillation. She had findings typical of mitral stenosis and no systolic precordial murmur. Her weight was 69 kg and her height was 173 cm. Cardiac catheterization confirmed mitral stenosis with a mean MV gradient of 12 mm Hg (cardiac output 3.15 liters/min) and an estimated MV area of 0.6 cm². The ejection fraction was 56% and the LV cavity was small (end-diastolic volume 48 ml). No aortic valve gradient was noted. Mild mitral regurgitation, trivial aortic regurgitation, and moderate pulmonary hypertension (pulmonary artery pressure 44/28 mm Hg) were noted. The patient underwent uncomplicated MV replacement with a Starr-Edwards model 6320 (size 2m) prosthesis.

In 1982, 10 years after MV replacement, catheterization was again performed to evaluate a systolic murmur that had become progressively louder over the past 7 years. A 2-dimensional echocardiogram (Fig. 1) showed normal motion of the poppet throughout the cardiac cycle. The prosthesis was positioned abnormally, with protrusion of the cage and ball into the LV outflow tract. At catheterization, the mean MV gradient was 8 mm Hg and there was no mitral regurgitation. Two slow pullbacks from left ventricle to aorta with an end-hole catheter (No. 8 Fr. right, Judkins USCI) showed

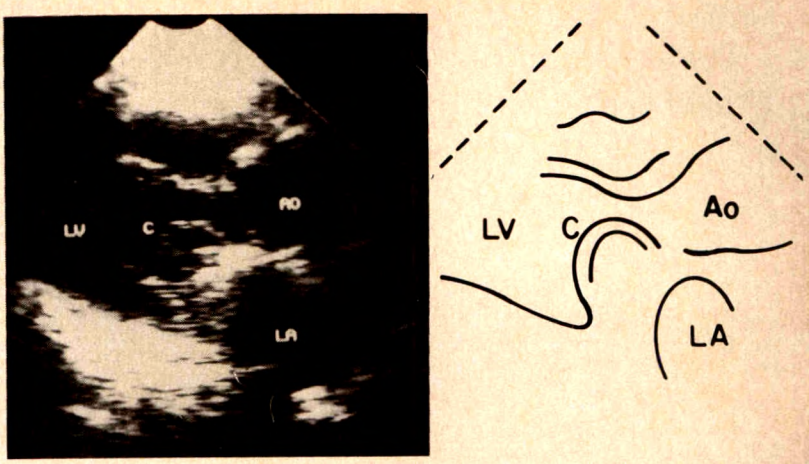

FIGURE 1. Two-dimensional echocardiogram and schematic reproduction in the left parasternal long-axis view. The prosthetic valve cage (C) projects into the outflow tract between the left ventricle (LV) and aorta (AO). The left ventricle and left atrium (LA) are of normal size.

a 50 to 70 mm Hg intraventricular gradient, well localized between the LV body and the subaortic valve outflow tract, corresponding to the position of the prosthetic MV ball and cage. There was no transvalvular aortic gradient (Fig. 2).

Despite previous suggestions that LV outflow obstruction could be caused by a Starr-Edwards MV prosthesis, this is the first report to confirm this phenomenon hemodynamically. The potential for LV outflow tract obstruction by such a prosthesis has been suggested by autopsy study,[1] preoperative echocardiography[2,3] and postoperative outcome.[4] As in our patient, 2-dimensional echocardiography may suggest the diagnosis by showing abnormal projection of the prosthesis into the LV outflow tract rather than into the body of the left ventricle. Continuous-wave Doppler ultrasound[5] may also aid in the diagnosis of such obstruction. At present, the diagnosis is still probably best confirmed by slow pullback with an end-hole catheter or, better yet, with a double sensor micromanometer.

Although LV outflow tract obstruction appears to be a rare complication of MV replacement with a Starr-Edwards mitral prosthesis, the development of a new systolic murmur should alert the cardiologist to differentiate LV outflow tract obstruction from valvular aortic stenosis, or even paravalvular or transvalvular regurgitation. The benign course of this patient over the 7 years after development of a new systolic murmur, with no development of LV hypertrophy, suggests that this may be a well tolerated lesion that does not necessitate surgery.

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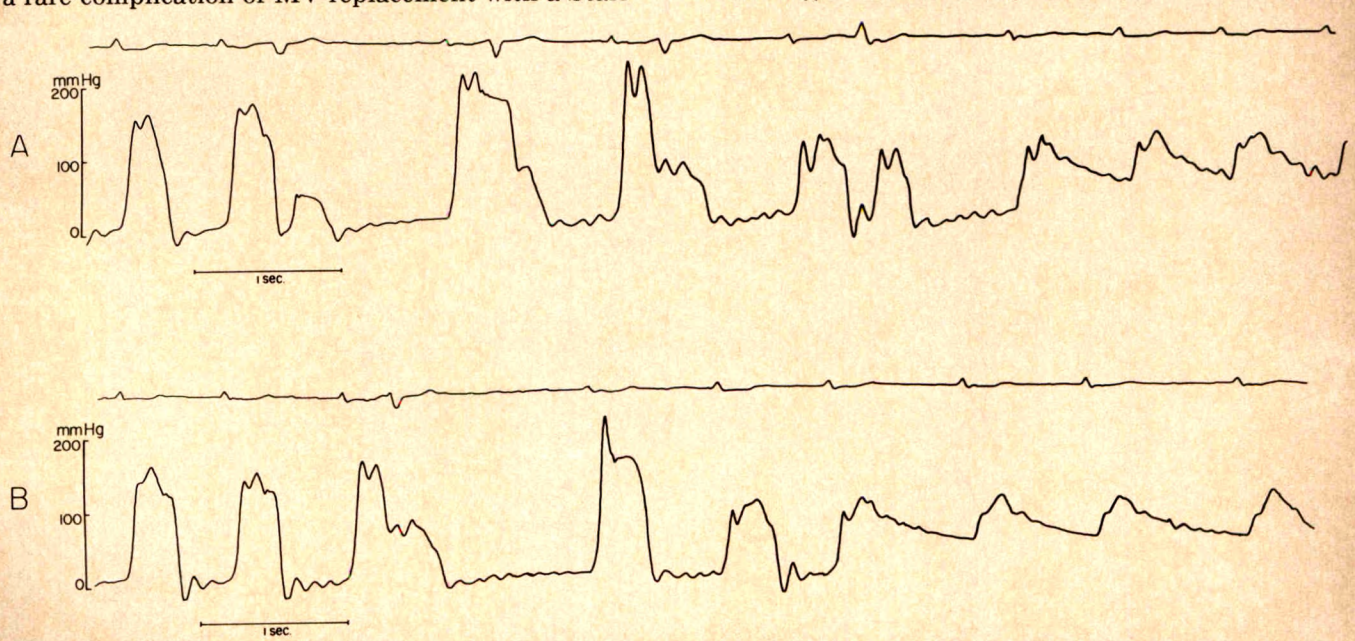

FIGURE 2. Tracings of pressures recorded on slow pullback from left ventricle to aorta with an end-hole catheter. Simultaneous ECG recordings displayed above each pressure tracing show atrial fibrillation with occasional premature beats. **A,** the last 3 beats are recorded in the aorta. The 2 beats before these are recorded in the outflow tract, with a systolic pressure equal to aortic systolic pressure, but with a diastolic pressure equal to left ventricular diastolic pressure. The seven systoles before these are recorded from the body of the left ventricle, demonstrating a systolic gradient between left ventricular body and outflow tract. **B,** the pullback sequence is repeated and demonstrates the same findings.

Cardiac Involvement by Gaucher's Disease Documented by Right Ventricular Endomyocardial Biopsy

WILLIAM D. EDWARDS, MD
HOWARD P. HURDEY III, MD
JAMES R. PARTIN, MD

We report a case in which a right ventricular endomyocardial biopsy specimen demonstrated Gaucher's cells in the myocardial interstitium. We are not aware of another instance of the biopsy diagnosis of cardiac Gaucher's disease.

A 34-year-old white woman with type 1 (chronic nonneuronopathic) Gaucher's disease had a history of splenectomy for massive splenomegaly, progressive hepatomegaly, recurrent myalgias and bone pain, and bilateral hip replacement for aseptic necrosis of the femoral heads. Unexplained systemic hypertension (150 to 195/95 to 115 mmHg), exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea and recurrent chest discomfort developed. An extensive noninvasive clinical workup failed to reveal the cause of her persistent hypertension. Cardiac catheterization, coronary arteriography and left ventriculography also failed to disclose a cause for the hypertension and cardiac symptoms. Multiple right ventricular endomyocardial biopsy specimens were procured. The patient's hypertension subsequently responded to medications, and she has since had no cardiopulmonary symptoms.

By light microscopy, the endomyocardial biopsy tissue revealed a normal endocardium and moderately hypertrophied myocardial cells. The myocardial interstitium was expanded by focal clusters of typical Gaucher's cells, which had blue-gray cytoplasm with routine hematoxylin-eosin staining and classic cytoplasmic striations with the periodic acid-Schiff base reaction and diastase predigestion (Fig. 1, A and B). By transmission electron microscopy, interstitial Gaucher's cells were distended by ellipsoid and needle-shaped membrane-bound lysosomal cytoplasmic sacs that contained twisted and filamentous deposits in a granular matrix (Fig. 1, C and D).

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Gaucher's disease is associated with storage of the sphingolipid glucocerebroside within the phagocytes of the reticuloendothelial system.[1,2] Involvement of the central nervous system forms the basis for 3 clinical subgroups (chronic nonneuronopathic, acute neuronopathic and subacute neuronopathic).[3] A bleeding disorder is often observed.[1] Furthermore, Gaucher's disease may involve the kidneys, lungs and heart, although cardiac involvement is usually manifested as hemorrhagic pericarditis.[4] Nevertheless, Gaucher's cells have been identified in the myocardial interstitium in autopsy specimens and, in 1 case, involved the left ventricle more extensively than the right ventricle.[4]

We report the right ventricular endomyocardial biopsy features in a woman with Gaucher's disease and unexplained hypertension, dyspnea and chest discomfort. Typical Gaucher's cells were identified in the myocardial interstitium but were not considered responsible for this patient's cardiac symptoms. Nevertheless, because endomyocardial biopsy is a safe and well-established clinical procedure that is ideally suited for the evaluation of storage diseases,[5] it may be indicated in patients with Gaucher's disease who have cardiac symptoms of undetermined cause.

Acknowledgment: The authors acknowledge John Kernan, MD, for the referral of this patient.

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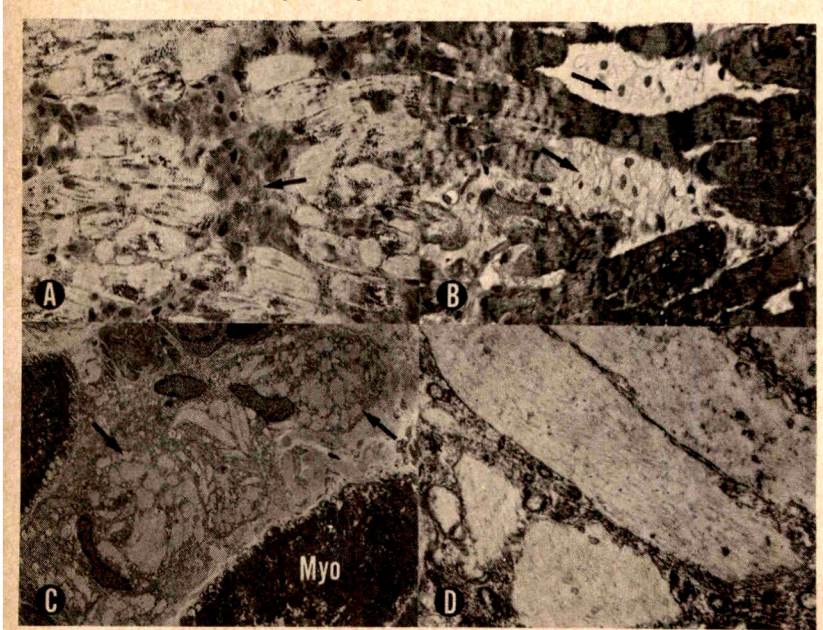

FIGURE 1. Photomicrographs of Gaucher's cells in endomyocardial biopsy specimen. **A** and **B,** appearance on light microscopy. Clusters of Gaucher's cells (**arrows**) demonstrate typical cytoplasmic striations by periodic acid-Schiff base reaction in paraffin-embedded tissue (**A** magnification ×300, reduced 36%) and pale cytoplasmic deposits by toluidine blue stain in plastic-embedded tissue (**B** magnification ×300, reduced 36%). **C** and **D,** appearance on transmission electron microscopy. Gaucher's cells (**arrows**), in the myocardial interstitium, contain ellipsoid and needle-shaped membrane-bound lysosomal sacs (**C** magnification ×2,000, reduced 36%) that are filled with irregular filamentous deposits (**D** magnification ×30,000, reduced 36%). Myo = myocardial cell.

The AFORMED Phenomenon: A Proposed Etiology

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The alternating failure of response of mechanical to electrical depolarization (AFORMED) phenomenon was first described >10 years ago.[1] Although the physiologic effects and clinical significance of electromechanical dissociation have been studied, the cause of the phenomenon has not been investigated. This report describes our observations, which may help elucidate the etiology of this phenomenon.

We observed the AFORMED phenomenon in 3 open-chest mongrel dogs during experiments unrelated to this phenomenon. In these experiments, 20- to 25-kg dogs were anesthetized with sodium pentobarbital, cuffed endotracheal tubes were inserted, and the dogs were placed on a positive-pressure, volume-regulated Harvard respirator. The lungs were periodically hyperinflated to prevent atelectasis. The chest was opened through a median sternotomy. A fluid-filled NIH catheter was placed in the ascending aorta by retrograde arterial catheterization of the femoral artery. A Carolina Medical Electronics perivascular flow probe was positioned around the pulmonary artery to measure the pulmonary artery flow. A Millar Micro-tip pressure transducer (model PC-761) was inserted into the pulmonary trunk through a stab incision in right ventricular outflow tract for continuous recording of pulmonary artery pressure. Hypoxemia was induced by administering 14% oxygen and the effects of various receptor blockers were studied to elucidate the mechanism of hypoxic pulmonary hypertension. Each AFORMED episode occurred during the tachycardia phase that followed successful resuscitation of cardiac arrest. (Cardiac arrest occurred in some dogs during hypoxic phase of the experiment.) The electrocardiogram, aortic pressure and pulmonary artery flow were recorded continuously during the AFORMED episodes. Rapid intravenous administration of 2.0 ml of 10% calcium gluconate promptly abolished the AFORMED phenomenon, but it reappeared 10 to 15 minutes later. There was a consistent but short-lived response to calcium in each dog and in each episode of the AFORMED phenomenon. Intravenous lanatoside-C abolished the phenomenon after a 30-minute latent period. There were no recurrences of AFORMED after administering lanatoside-C during a 2- to 3-hour observation period in 2 dogs. When a faster-acting glycoside (*G. strophanthin*) was used in another dog, the AFORMED phenomenon was promptly abolished (Fig. 1). These observations suggest that the lack of availability of calcium, perhaps in the area of myofilament, is the cause of this phenomenon. The rationale for this is that the phenomenon could be abolished by increasing the calcium concentration or by augmenting the calcium influx[2] by the use of cardiac glycoside. Detailed studies of the ionic fluxes may clarify the role of calcium in the AFORMED phenomenon.

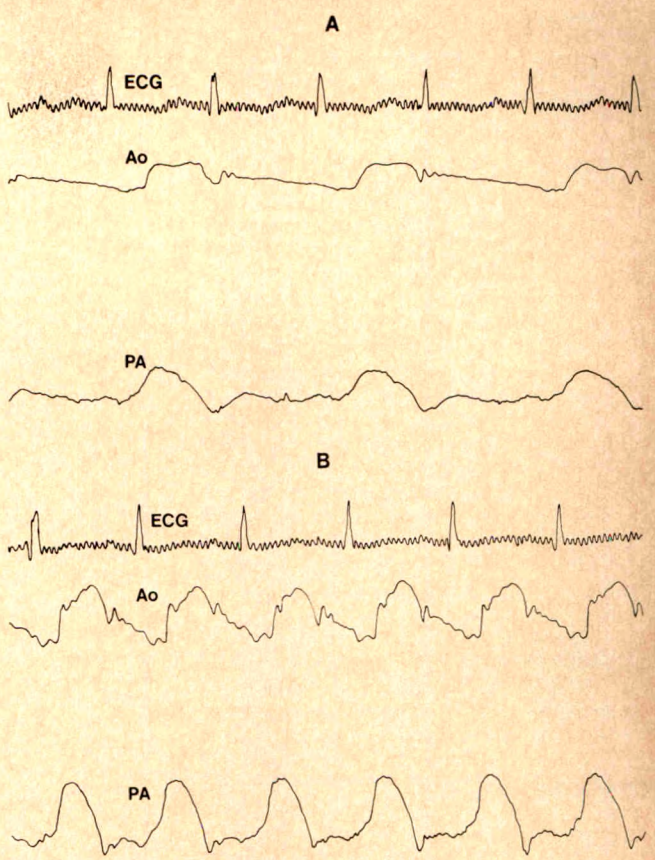

FIGURE 1. **A,** the aortic (Ao) pressure pulse follows every other QRS complex of the electrocardiogram (ECG). The pulmonary artery (PA) flow recording is also similar to aortic pressure response. This was recorded shortly after successful resuscitation of cardiac arrest. **B,** immediately after intravenous injection of *G. strophanthin*, the AFORMED phenomenon was abolished.

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From the Department of Pediatrics, Medical College of Georgia, Augusta, Georgia. Manuscript received January 25, 1983; accepted May 16, 1983.

LETTERS*

CARDIAC CATHETERIZATION IN ATHLETES

In the recent article by Oakley and Oakley,[1] the investigators concluded that exercise electrocardiography and echocardiography help to exclude organic heart disease, but left-heart catheterization is justified if doubt still exists.

Surprisingly, they did not even mention the role of nuclear cardiology or 2-dimensional echocardiography, especially since 6 of the 10 subjects were asymptomatic and achieved heart rates >150 beats/min. Cardiac catheterization was indicated in the subject who showed anterior Q waves and had palpitations.

Patterson et al[2] concluded that coronary angiography is not necessary to rule out the diagnosis of coronary artery disease in persons who have the 4 characteristics: (1) no clinical indicators of coronary disease, such as angina; (2) adequate exercise; (3) negative exercise electrocardiogram; and (4) negative exercise thallium images.

The addition of thallium to exercise electrocardiogram in Oakley and Oakley's patient's population would probably have eliminated the necessity of cardiac catheterization.

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Henry N. Wagner, Jr., MD
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MULTIPLE VERSUS SINGLE CORONARY ARTERIAL STENOSIS: HEMODYNAMIC DIFFERENCES

The study by Subbah and Stein points out 1 difficulty in evaluating hemodynamic severity of coronary artery stenoses if only the percentage of coronary diameter reduction is used.[1] Their study shows in an in vitro system how multiple coronary stenoses in 1 vessel can have a greater effect on coronary flow than a single stenosis of equal diameter reduction and length. The authors also found that lengthening a 50% coronary diameter reduction from 2–6 mm had little effect on the magnitude of coronary flow reduction. This last point seems to be in slight discrepancy with our findings.[2–4]

We found in dogs that lengthening coronary stenoses of 40 to 60% diameter reduction does affect coronary flow. These effects were most pronounced during coronary vasodilation occurring after transient coronary occlusion. In their in vitro system, Sabbah and Stein did not find increasing the length of a 50% stenosis by a factor of 3 produced important changes. In open-chest dogs, we found during vasodilation a 9% decrease in flow as the length of 40–60% coronary stenoses were increased from 1 to 3 mm. More prominent effects on coronary flow were seen as narrowing length was increased from 5 to 15 times (i.e., from 1 to 5, 10 to 15 mm) both during vasodilation and at rest. These findings agree with those of Friesinger and Hillis,[5] who also evaluated in an in vivo model the effect of longer stenoses than did Sabbah and Stein. Therefore, the differences observed concerning the importance of coronary stenoses length may be because of the longer lengths (i.e., up to 10 and 15 mm) and relative change in stenosis length (i.e., by factors of 2, 3, 5, 10 and 15) we used.

We also studied the effects of multiple coronary stenoses on 1 vessel and compared them to single stenoses of similar total length in open-chest dogs.[3,4] Our in vivo results were similar to the in vitro findings of Sabbah and Stein. We found that 40–60% diameter reductions 2–3 mm long did not reduce resting flow or increase the pressure gradient across them. Multiple 1-mm-long stenoses consistently produced small resting pressure gradients. Additionally, during vasodilation produced by transient coronary occlusion, 2 or 3 stenoses decreased coronary flow more than 1 stenosis of similar total length.

Robert L. Feldman, MD
W. W. Nichols, PhD
Carl J. Pepine, MD
C. Richard Conti, MD

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BASIC REQUIREMENTS FOR INVESTIGATING SYSTOLIC TIME INTERVALS

Carroll et al[1] have contributed an outstanding report on serial changes in left ventricular (LV) function after correction of chronic aortic regurgitation. As with most letters to the editor, this is not so much to criticize the authors' work so much as the review process ("revision accepted" implies eagle-eyed reviews). Here, reviewers familiar with systolic time intervals should have caught 2 important methodologic omissions: heart rate (HR) influence, particularly correction of the preejection period (PEP) and other systolic intervals (STIs), and consideration of the patients' therapeutic status.

Considerable "standard" literature insists on the necessity to rate-corrected PEP. Yet, a great deal of work (summarized in references 2 to 4) indicates that PEP is either negligibly related to HR or, at best, related with very low correlation coefficients of borderline significance. Regardless of the levels of correlation, many workers consider that failure of PEP to change during atrial pacing—virtually "pure" HR effect—makes even statistically significant HR-PEP associations physiologically spurious. (Pacing does reduce LV ejection time [LVET] and, consequently, QS_2.) In fairness, those working in the field have not come to a consensus; moreover, correction factors (slope of the linear regression) for ejection time and QS_2 are not the same for all investigators. Thus, in every report of STIs it is methodologically necessary to insist on including HR data. This permits those who differ on these points to recalculate the results and examine them in the light of their own results and conceptual preferences. I should like to ask the authors to provide the HRs corresponding to their data in their Table III. Finally, and in fairness, I have observed that when PEP is used without rate correction, directional results are almost always the same as when some rate correction ("PEP index") is used, although significance levels may differ owing to contribution by larger or smaller HR and, presumably, departures from linearity. This observation may explain why no strong effort has been made to resolve the appropriateness of PEP "correction" for HR.

Another inescapable consideration is the patients' therapeutic status. STIs are sensitive to a wide variety of pharmacologic agents. Some of these patients may have been taking digitalis, which variably shortens the STI. Therefore, mention should be made of the patients' medication in each group and whether results differed within a given group for those taking digitalis or any other agent that affects the STI.

David H. Spodick, MD, DSc
Worcester, Massachusetts

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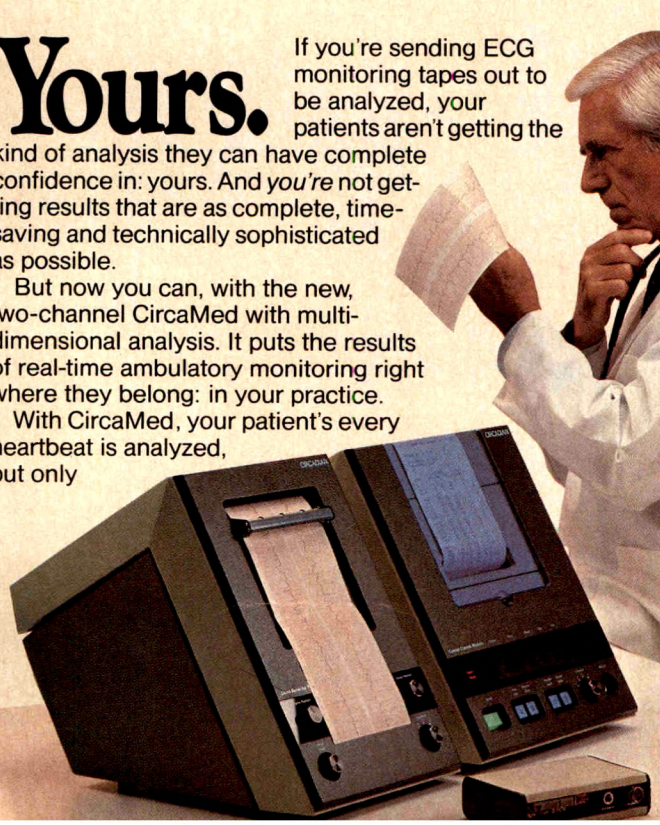

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Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS—**1. Hypotension:** Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL (bretylium tosylate) should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY—The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN—The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS—**1. Dilution for Intravenous Use:** BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use of Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function.

ADVERSE REACTIONS—Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

HOW SUPPLIED—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP. pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, non-pyrogenic.

Oct. 1980

Please refer to complete prescribing information prior to use.

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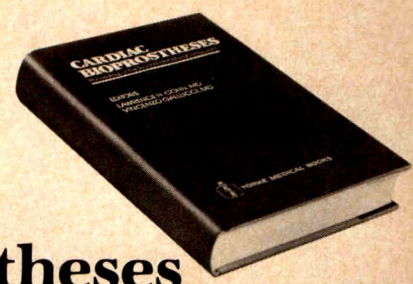

Cardiac Bioprostheses

Proceedings of the Second International Symposium Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609 pp., illus., Nov. 1982., $65.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much *current* information on the field of cardiac valves.

Almost 20 years have gone by since the first reports of homograft valve replacement by Drs. Donald Ross and Brian Barratt-Boyes and almost 10 years since the first reports began to appear about commercially available, quality-controlled porcine bioprosthetic and bovine pericardial valves. This book brings you completely up-to-date on what has happened since and what is happening *today*.

If your interests include the clinical, pathological and bioengineering aspects of cardiac bioprostheses then this book is a *must buy!* It should not be missing from your own professional library.

Who are the editors?

Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of *Modern Techniques in Surgery* and co-author of the new annual, *Cardiology*, now available in its second issue, *Cardiology 1982*.

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

• Section 1 CLINICAL ANALYSIS • Section 2 HEMODYNAMICS • Section 3 THROMBOEMBOLISM • Section 4 PEDIATRIC VALVE REPLACEMENT • Section 5 EXPERIMENTAL PATHOLOGY • Section 6 EXPLANT PATHOLOGY • Section 7 BIOPROSTHETIC BIOENGINEERING • Section 8 LONG-TERM FOLLOW-UP • Section 9 SUMMING UP • AUTHOR INDEX • SUBJECT INDEX

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metoprolol tartrate

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New Dosage Schedule: To start, 100 mg once-a-day, or in divided doses. Lower doses (especially 100 mg) may not maintain full effect at end of 24-hour period. Measure BP near end of dosing interval, adjust to larger or more frequent dosage if needed.

*exerts a relative preference for beta-one receptors; this preference is not absolute.

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

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Please see next page for brief summary of Prescribing Information.

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Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Tablets of 50 mg
Tablets of 100 mg

Prescribing Information

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage In Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 100 mg daily in single or divided doses whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Consult complete product information before prescribing.

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CME Test #3: Answer Sheet

Effect of Interventions in Salvaging Left Ventricular Function in Acute Myocardial Infarction: A Study of Intracoronary Streptokinase

Instructions: Mark the appropriate box with an "X."
Test Questions appear on page 643.

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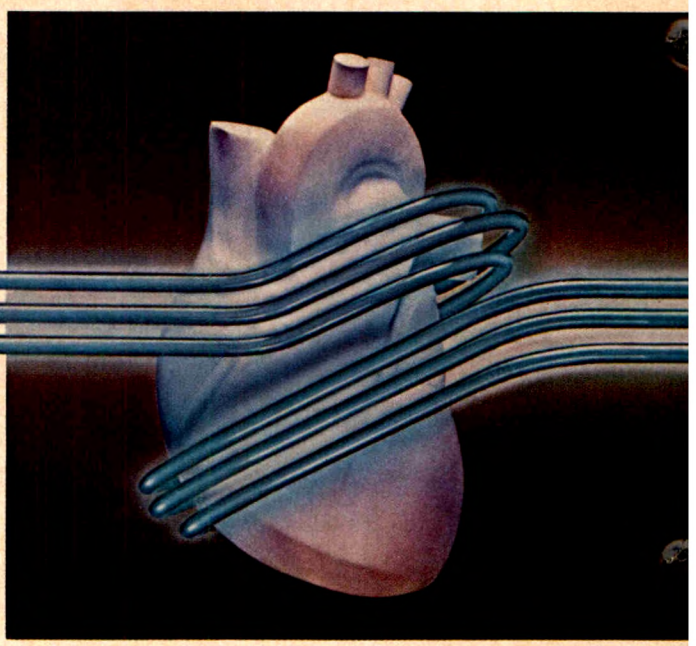
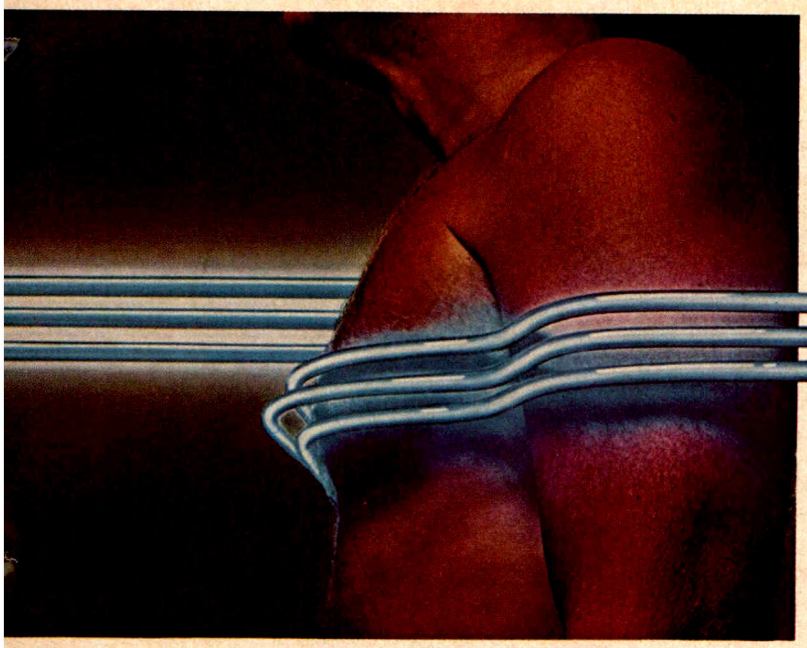


The cardiovascular protection of INDERAL—for simplified core therapy in angina

Once-daily INDERAL LA (propranolol HCl) adds simplicity and convenience to the therapeutic benefits of INDERAL in the long-term treatment of angina.

INDERAL LA provides smooth, 24-hour beta blockade with single daily dosing–to reduce the frequency and severity of anginal attacks around the clock. As core therapy, INDERAL LA is compatible with other conventional antianginal therapies.

Like INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.



THE ONE™ TO COUNT ON

Start with 80 mg once daily...

Simplified core therapy begins with 80 mg once daily. Although individual patients may respond to various doses, the average optimal dose in angina pectoris is 160 mg once daily.

When converting patients from other beta blockers, including INDERAL tablets, switch to the nearest milligram equivalent of INDERAL LA once daily and evaluate clinical results to determine if dosage adjustment is necessary. For arrhythmias, use conventional INDERAL (propranolol HCl) tablets.

80 mg 120 mg 160 mg

The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

Please see next page for brief summary of prescribing information.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

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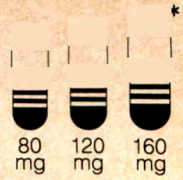

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)*
INDERAL® LA BRAND OF propranolol hydrochloride
(Long Acting Capsules)
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta-blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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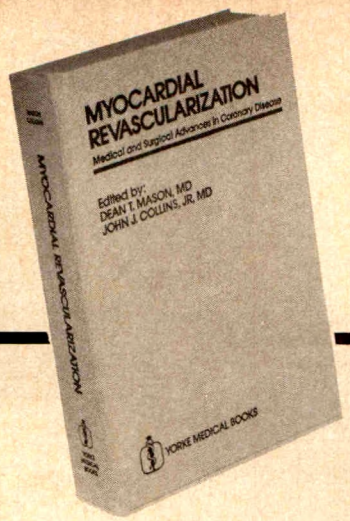

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Section 2 - Variant Angina Pectoris

Section 3 - Unstable Angina Pectoris

Section 4 - Acute Myocardial Infarction

Section 5 - Myocardial Preservation

Section 6 - Pharmacologic and Related Approaches to Coronary Dilatation

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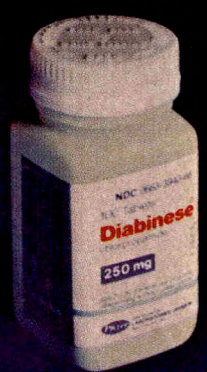

When choosing a therapeutic regimen to treat Non-Insulin-Dependent Diabetes Mellitus (NIDDM), many factors should be considered, including the patient's age, mental state, concomitant medication, and illnesses.

*As with all sulfonylureas, hypoglycemia may occur with Diabinese, but less frequently than with insulin therapy.

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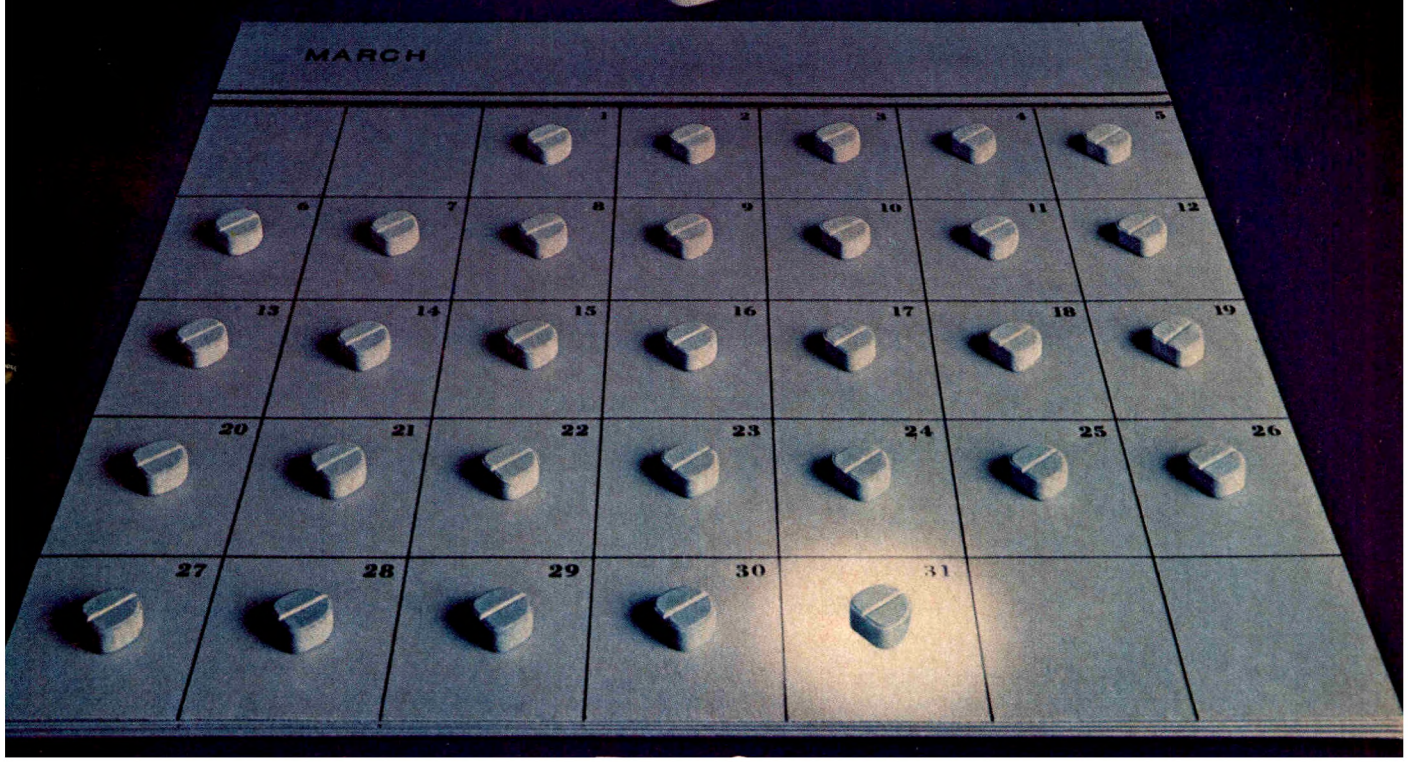

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Diabinese is contraindicated in patients with serious impairment of hepatic, renal, or thyroid function.
Precautions: Use chlorpropamide with caution with barbiturates, in patients with Addison's disease or in those ingesting: alcohol, antibacterial sulfonamides, thiazides, phenylbutazone, salicylates, probenecid, dicoumarol or MAO inhibitors. Adequate dietary intake should be assured in all patients using Diabinese.
Warnings: DIABINESE (CHLORPROPAMIDE) SHOULD NOT BE USED IN JUVENILE DIABETES OR IN DIABETES COMPLICATED BY ACIDOSIS, COMA, SEVERE INFECTION, MAJOR SURGICAL PROCEDURES, SEVERE TRAUMA, SEVERE DIARRHEA, NAUSEA AND VOMITING, ETC. HERE, INSULIN IS INDISPENSABLE.
HYPOGLYCEMIA, IF IT OCCURS, MAY BE PROLONGED. (SEE ADVERSE REACTIONS.) IN INSTANCES OF CONCOMITANT USE WITH INSULIN, PATIENTS SHOULD BE CAREFULLY MONITORED.
Adverse Reactions: Usually dose-related and generally respond to reduction or withdrawal of therapy. Generally transient and not of a serious nature and include anorexia, nausea, vomiting and gastrointestinal intolerance; weakness and paresthesias.
Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occasionally occurred, including jaundice, skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood. They occur characteristically during the first six weeks of therapy. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug. The more severe manifestations may require other therapeutic measures, including corticosteroid therapy. Diabinese should be discontinued promptly when the development of sensitivity is suspected.
Jaundice has been reported, and is usually promptly reversible on discontinuance of therapy. THE OCCURRENCE OF PROGRESSIVE ALKALINE PHOSPHATASE ELEVATION SHOULD SUGGEST THE POSSIBILITY OF INCIPIENT JAUNDICE AND CONSTITUTES AN INDICATION FOR WITHDRAWAL OF THE DRUG.
Leukopenia, thrombocytopenia and mild anemia, which occur occasionally, are generally benign and revert to normal, following cessation of the drug.
Cases of aplastic anemia and agranulocytosis, generally similar to blood dyscrasias associated with other sulfonylureas, have been reported.
BECAUSE OF THE PROLONGED HYPOGLYCEMIC ACTION OF DIABINESE, PATIENTS WHO BECOME HYPOGLYCEMIC DURING THERAPY WITH THIS DRUG REQUIRE CLOSE SUPERVISION FOR A MINIMUM PERIOD OF 3 TO 5 DAYS, during which time frequent feedings or glucose administration are essential. The anorectic patient or the profoundly hypoglycemic patient should be hospitalized.
Rare cases of phototoxic reactions have been reported.
Edema associated with hyponatremia has been infrequently reported. It is usually readily reversible when medication is discontinued.
Dosage: The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally, cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED. The mild to moderately severe, middle-aged, stable diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on smaller amounts of Diabinese, in the range of 100 to 125 mg daily.
After five to seven days following initiation of therapy, dosage may be adjusted upward or downward in increments of 50 to 125 mg at intervals of three to five days. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 MG DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. Maintenance doses above 750 mg daily should be avoided.
Supply: 100 mg and 250 mg, blue, 'D'-shaped, scored tablets.

More detailed professional information available on request.

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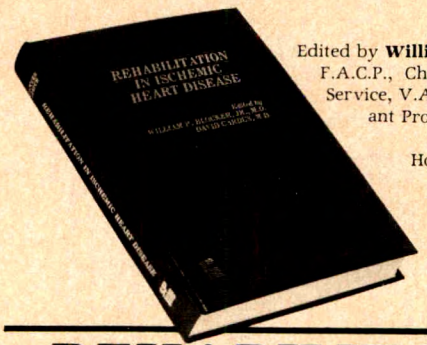

Edited by **William P. Blocker, Jr., M.D.,** F.A.C.P., Chief, Rehabilitation Medicine Service, V.A. Hospital, Houston, Assistant Professor of Physical Medicine, Baylor College of Medicine, Houston, and **David Cardus**, M.D., F.A.C.C., Professor of Physiology and Rehabilitation, Baylor College of Medicine, Houston, Texas.

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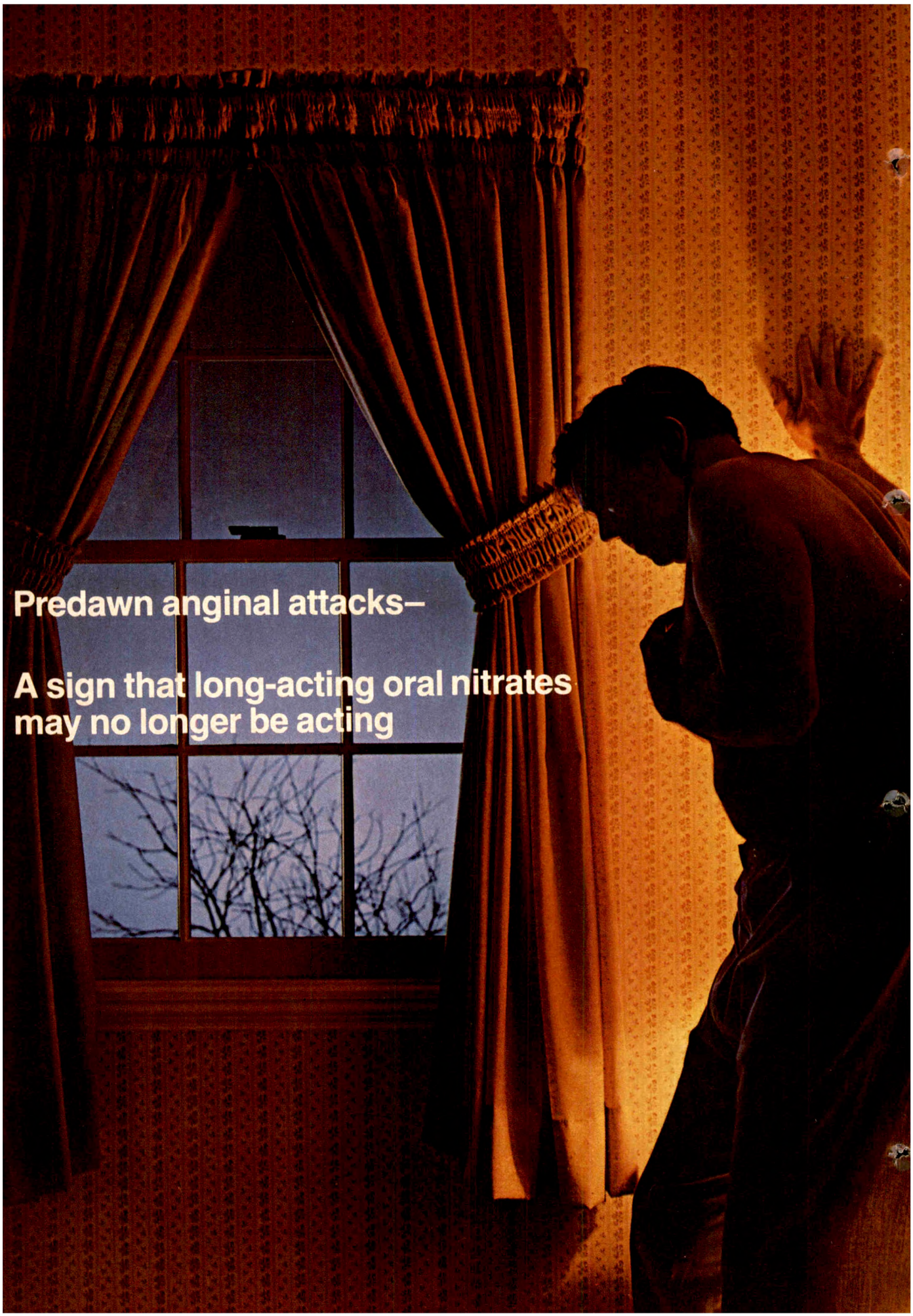
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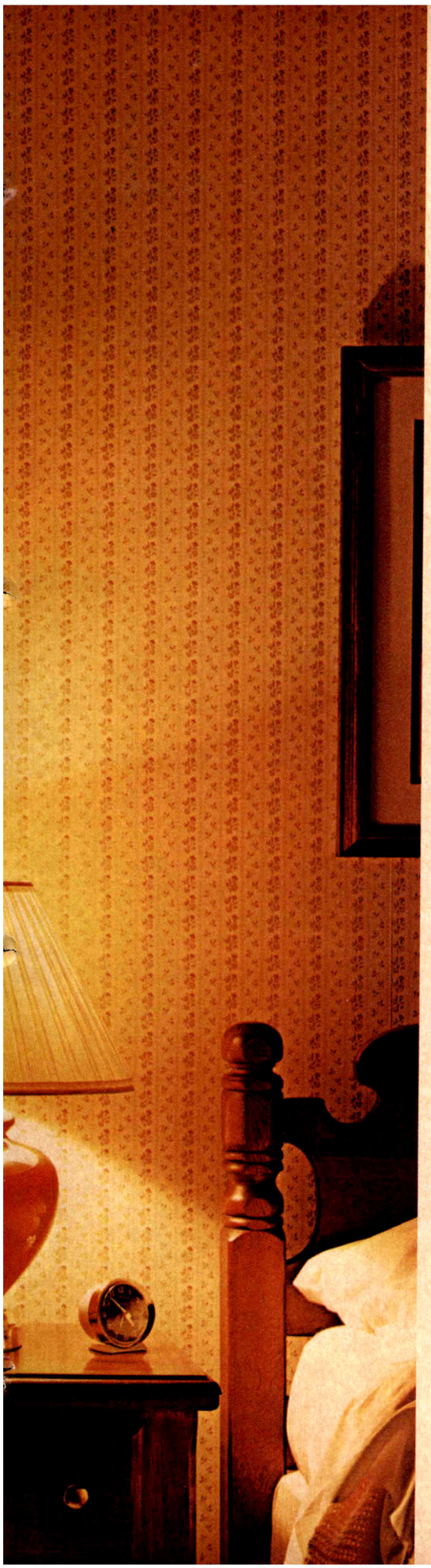
A sign that long-acting oral nitrates may no longer be acting



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Side effects include transient headaches and orthostatic hypotension.
Contraindicated in patients with increased intraocular pressure. Withdrawal from treatment should be gradual.

Please read Brief Summary of Prescribing Information.

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Brief Summary of Prescribing Information.

INDICATIONS AND USAGE
Transderm-Nitro system is indicated for the prevention and treatment of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and or hemodynamic monitoring.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.

Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

Consult complete product information before prescribing.

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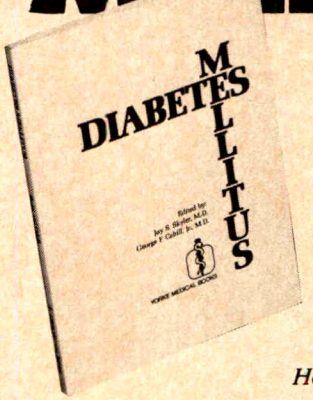

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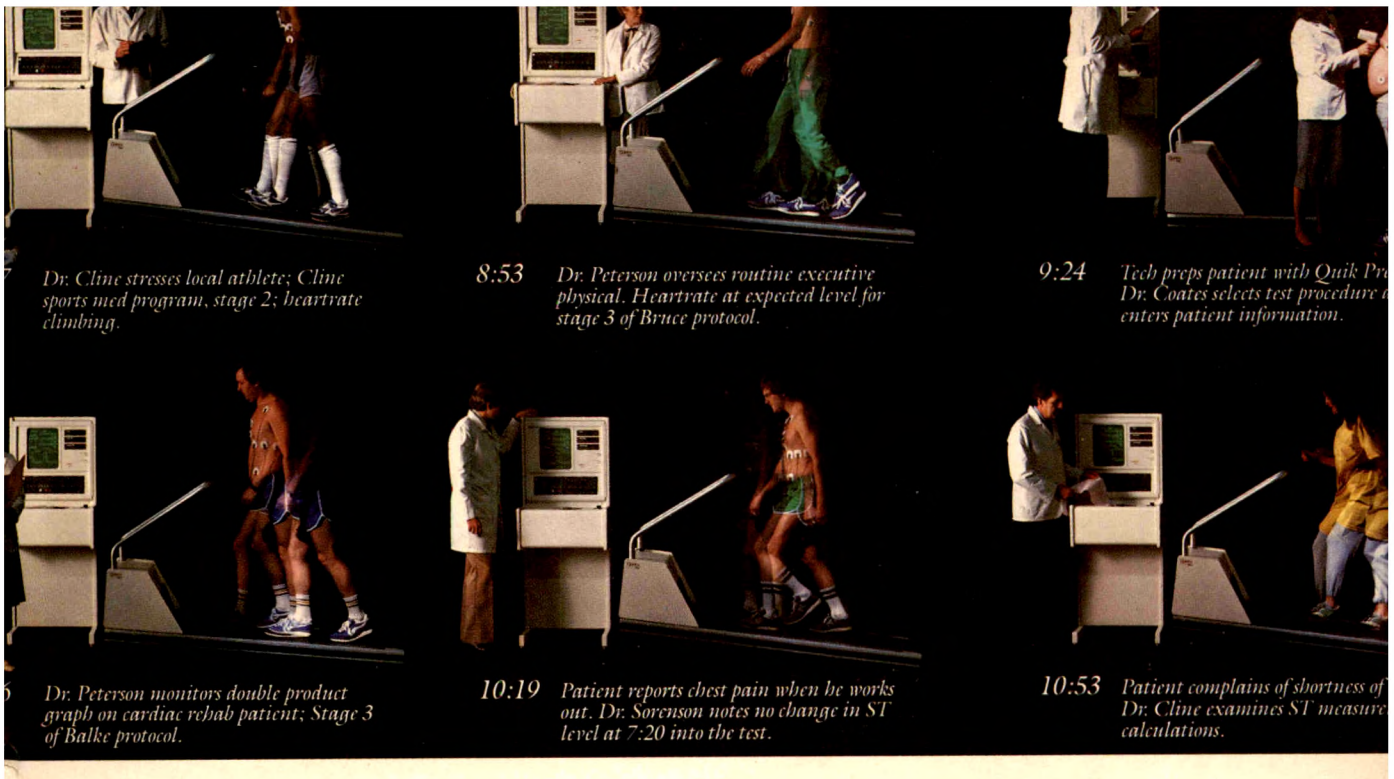

Dr. Cline stresses local athlete; Cline sports med program, stage 2; heartrate climbing.

8:53 *Dr. Peterson oversees routine executive physical. Heartrate at expected level for stage 3 of Bruce protocol.*

9:24 *Tech preps patient with Quik Pr... Dr. Coates selects test procedure ... enters patient information.*

Dr. Peterson monitors double product graph on cardiac rehab patient; Stage 3 of Balke protocol.

10:19 *Patient reports chest pain when he works out. Dr. Sorenson notes no change in ST level at 7:20 into the test.*

10:53 *Patient complains of shortness of ... Dr. Cline examines ST measure... calculations.*

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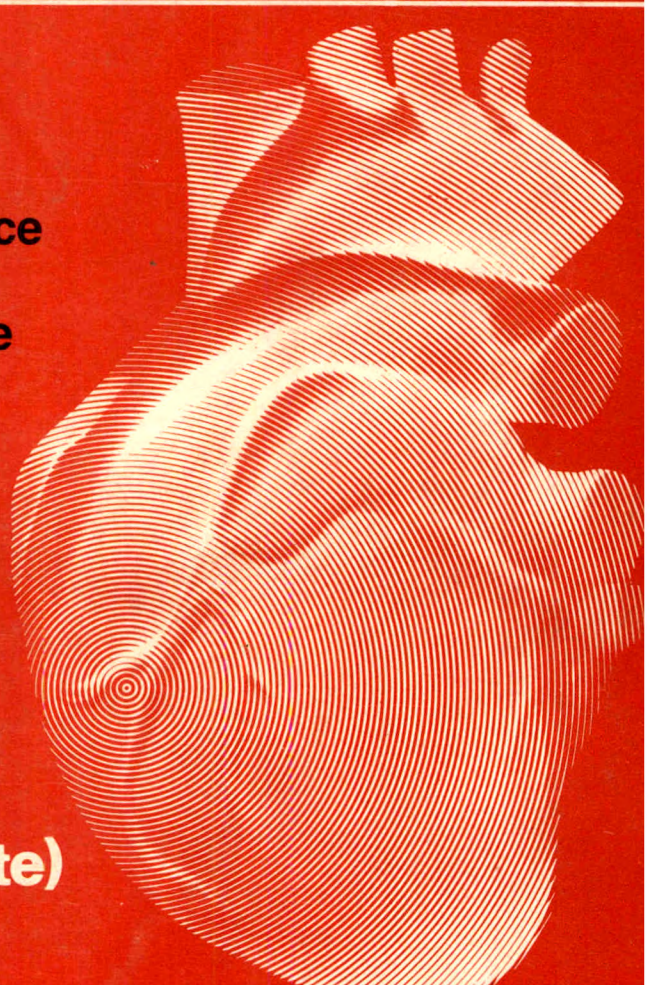

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE:

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreas excretion of quinidine.
With coumarin anticoagulants	Reduction of clotting factor concentrations
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
With digoxin	Increased plasma concentrations of digox (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases whe the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: Th drug should be used with caution due to excretion of the quinidine in breast milk. ADVERS REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/ disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTES TINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QR complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricul tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMA TOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranul cytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, an syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasi blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, nig blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intens pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episod vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribin Information.

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Symposium on Perspectives on the Treatment of Ventricular Arrhythmias

Donald C. Harrison, MD, Guest Editor

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SYMPOSIUM ON PERSPECTIVES ON THE TREATMENT OF VENTRICULAR ARRHYTHMIAS

Guest Editor: Donald C. Harrison, MD

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Metabolites of antiarrhythmic drugs are frequently important for their action and toxicity. The presence of active metabolites can be inferred from variability of response to steady-state therapeutic plasma concentrations. In some cases, metabolites may accumulate to toxic levels during heart, renal or hepatic failure. Therefore, direct evaluation of metabolites is indicated when they are known. Procainamide, quinidine, disopyramide, verapamil, encainide and lorcainide are drugs whose metabolites are under study.

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ROBERT E. KATES

Therapeutic plasma concentration guidelines have been proposed for most antiarrhythmic drugs. The relation between measured plasma concentration and effect is well characterized for only a few drugs, and it is recognized that several factors influence this relation. These factors include serum protein binding, active metabolites, intrinsic responsiveness and myocardial accumulation. Interpretation of plasma concentration of antiarrhythmic drugs also requires consideration of pharmacokinetic factors. Plasma drug levels can be useful only when dosing history and timing of the sample relative to drug administration are considered. Despite several limitations, plasma concentration monitoring of antiarrhythmic drugs can be helpful if evaluated with an understanding of the pharmacokinetics of the drug being measured, the clinical status of the patient, and an appreciation of the factors that may influence the relation between the measured level and the resultant clinical response.

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PAUL J. BLOCK and ROGER A. WINKLE

It is important to understand the hemodynamic effects of the antiarrhythmic drugs in order to use them safely. Many of these drugs have a direct effect on myocardial performance as well as on the peripheral capacitance and resistance vessels. The net effect of a drug often depends on the balance between these direct actions and reflex and other autonomically mediated drug effects. This report reviews the in vitro and in vivo hemodynamic data available for each of the frequently used antiarrhythmic drugs. These data and their clinical implications are discussed.

24C Clinical Profiles of Newer Class I Antiarrhythmic Agents—Tocainide, Mexiletine, Encainide, Flecainide and Lorcainide

ANTHONY POTTAGE

Potency is only 1 factor that determines the clinical value of an antiarrhythmic agent. Electrophysiologic and hemodynamic effects that compromise safety are clearly undesirable, as are other adverse effects that limit safety or patient acceptability. Pharmacokinetic properties that allow various routes of administration and predictable

behavior in a broad spectrum of patients are an advantage. New class I antiarrhythmics—tocainide, mexiletine, encainide, flecainide and lorcainide—have been developed in a search for increased potency, fewer cardiac and noncardiac adverse effects, and pharmacokinetics that allow greater flexibility of use. Some are remarkably effective for short-term use and are virtually free of dose-related adverse effects. Others have pharmacokinetic properties that allow predictable use in a variety of clinical settings. Although none of the newer agents reliably suppresses all arrhythmias in all patients, their differing electrophysiologic effects and pharmacokinetic properties extend the range of options available for individualization of therapy in the patient at risk.

32C Effect of Antiarrhythmic Drugs on Mortality After Myocardial Infarction

CURT D. FURBERG

Antiarrhythmic drugs have theoretical potential for prevention and prophylaxis of ventricular arrhythmias in patients with coronary heart disease. However, randomized, controlled clinical trials have not demonstrated conclusive effects on survival. This may be because they do not improve prognosis, because insufficient design methods obscure a favorable intervention effect which does occur, or because drugs help some patients while harming others and thereby confound the results. Of 20 clinical trials, ventricular arrhythmia as an entry criterion occurred in only 1; all trials were small. Increasing attention to methods will permit better-designed trials.

37C Methods for Documenting Antiarrhythmic Efficacy

DONALD C. HARRISON

Although several methods have been suggested for demonstrating the efficacy of antiarrhythmic agents, no single method has been fully accepted by clinical investigators. Spontaneous variability in the occurrence of arrhythmias in individual patients makes assessment of individual response difficult, but the relative comparability of average frequency and complexity within groups presents investigators with an opportunity to determine, over time, an average response. Establishing expected responses and variations from that with confidence intervals by a new statistical approach using linear regression analysis appears promising. Continued research for establishing widely acceptable methods is required.

41C Role of Electrophysiologic Techniques in the Selection of Antiarrhythmic Drug Regimens for Ventricular Arrhythmias

JEREMY N. RUSKIN, MARK H. SCHOENFELD, and HASAN GARAN

Programmed electrical stimulation of the heart provides a useful new technique for guiding the selection of antiarrhythmic drug regimens in selected patients with ventricular tachycardia (VT) or ventricular fibrillation. The technique of programmed electrical stimulation has been applied successfully in patients with recurrent sustained VT, out-of-hospital ventricular fibrillation and unexplained syncope in the presence of structural heart disease. The complete suppression with a drug regimen of VT induced by programmed electrical stimulation is highly predictive of freedom from both recurrent VT and sudden death. In addition, this technique appears to hold promise as a means of assessing the arrhythmogenic effects of antiarrhythmic drugs in selected patients.

47C Definition of Benign Versus Malignant Ventricular Arrhythmias: Targets for Treatment

J. THOMAS BIGGER, Jr.

The prevalence and clinical significance of ventricular arrhythmias determine their need for treatment. The clinical significance is greater with advancing age, severity of heart disease and ventricular hypertrophy. The most malignant arrhythmias are out-of-hospital ventricular fibrillation, recurrent sustained ventricular tachycardia, and torsades de pointes ventricular tachycardia. Potentially malignant arrhythmias are well defined only in the post–myocardial infarction patients. In these patients, ventricular premature complexes have independent prognostic significance when they are more frequent than 10 per hour. Benign ventricular arrhythmias are common in patients with no heart disease.

55C Treatment and Prophylaxis of Ventricular Arrhythmias in Acute Myocardial Infarction

RONALD W. F. CAMPBELL

Antiarrhythmic drug use in acute myocardial infarction has undergone major changes in the last 20 years. Selective and unselective prophylactic drug administration and drug use only for established life-threatening arrhythmias are the 3 major strategies in current use. Each has limitations and none is ideal. New evidence regarding the natural history of arrhythmias during the coronary care unit phase of infarction suggests that reappraisal of the goals of electrocardiographic monitoring is required. Further research and investigation of arrhythmia management in the acute phase of myocardial infarction is hampered by ethical and scientific considerations but is sufficiently important to warrant finding ways to perform new studies.

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Symposium on Perspectives on the Treatment of Ventricular Arrhythmias

Donald C. Harrison, Guest Editor

Introduction

DONALD C. HARRISON, MD

This symposium contains presentations made by a distinguished faculty at a symposium entitled, "Perspectives on the Treatment of Ventricular Arrhythmias," held March 19, 1983, in New Orleans, Louisiana. A group of experts was assembled to present the new and exciting work that is taking place. The meeting and the publication of the reports presented are supported by an educational grant from Merck Sharp & Dohme.

The objectives and goals for the symposium included presenting the state-of-the-art methods for treating ventricular arrhythmias, focusing on coupling basic science with clinical applications, and the diagnosis, classification and treatment of this common malady affecting patients with heart disease. The pharmacodynamic and pharmacokinetic profile of existing drugs and newer antiarrhythmic drugs were the focus of several presentations. In addition, 2 speakers identified the patients with ventricular arrhythmias who could not be treated. Finally, it was our purpose to provide study designs for assessing the efficacy and safety of the new agents that are being introduced on an almost daily basis.

Clinical Background

Cardiovascular disease killed more than 1 million persons in the United States last year. This represented 51% of all deaths; of these, approximately 350,000 patients experienced sudden cardiac death, which the evidence to date suggests was due to ventricular arrhythmias. In recent years, the number of patients with serious ventricular arrhythmias seen by cardiologists appears to be increasing. The reasons for this increase are unclear, but may relate to 4 factors. First, monitoring techniques are available for the detection of arrhythmias in a much broader group of patients with coronary heart disease. Ambulatory monitoring, computer-based, in-hospital monitoring systems, and phone transmission of electrocardiograms all permit a higher degree of monitoring. Second, more patients with serious ventricular function are surviving myocardial infarction as a result of improved care. These persons are more prone to develop serious and life-threatening ventricular arrhythmias. Third, resuscitation of persons who experience sudden death out of the hospital is becoming much more common. These persons represent a pool of arrhythmia patients seen by the cardiologist. Fourth, patients and physicians are more aware of what I have termed "cosmetic arrhythmias," which may be noted on an electrocardiogram or an ambulatory monitoring device but do not have serious consequences or prognostic implications.

Since arrhythmias are seen with greater frequency, the public and physicians are more aware of antiarrhythmic drugs and their potential for preventing sudden cardiac death.

Modified Classification of Antiarrhythmic Agents

In the symposium, 2 factors receive serious consideration. The first is a modification of the existing classification schemes for antiarrhythmic agents. Vaughan Williams devised a 4-level classification scheme based upon cellular electrophysiologic observations. Class I agents have local anesthetic action and affect fast sodium channels; the prototypical agent is quinidine.

From the Cardiology Division, Stanford University School of Medicine, Stanford, California.

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Class II agents are beta-adrenergic blocking drugs, including selective and nonselective agents. Propranolol is generally considered the prototype agent. Class III agents are those that prolong the action potential repolarization phases. Amiodarone is usually considered the prototype for this group. Class IV drugs are calcium-channel blocking agents that have cardiac effect; verapamil is usually considered the prototype drug.

Many new agents obviously fall into the Vaughan Williams class I group. I recently devised a scheme of expanding the class I agents into subgroups. Table I is an outline of a modified class I schema based upon electrophysiologic studies in cells and in man together with a clinical profile. I believe that this modified system permits a means of thinking about the new agents we encounter.

All classification schemes are arbitrary and may be challenged. However, for ease of thinking and some practical points about combination therapy in patients, such a modified class I scheme seems useful. In treating patients with combined therapy, class Ia should be combined with class Ib, or class Ic should be combined with class Ib. Class Ia and Ic drugs probably should be given in combination only carefully.

TABLE I Modified Class I Based on Electrophysiologic and Clinical Profiles

Class	Action	Prototype Drugs
Ia	Depress phase 0 of the action potential	Quinidine
	Prolong repolarization	Procainamide
	Slow conduction, moderately	Disopyramide
Ib	Little effect on phase 0 of the action potential	Lidocaine
	Shorten repolarization	Mexiletine
	Increase fibrillation threshold	Tocainide
Ic	Markedly depress phase 0 of the action potential	Encainide
	Slight effect on repolarization	Flecainide
	Profound slowing conduction	Lorcainide

Methods of Assessing Efficacy of Antiarrhythmic Drugs

During the past several decades, considerable controversy has developed regarding the means of assessing the efficacy of antiarrhythmic drugs. There is no ideal way, but 3 subcategories of response might be considered.

First are population studies. It is frequently easy to average the response of a group of patients. This average response may be in controlled trials of the agent under study against a placebo; it may be a comparative trial of the new agent with a standard agent, or it may be in a parallel-designed field trial, with death or recurrence of serious arrhythmias as endpoints.

Second, studies may be performed in individual patients. Because of the high likelihood of spontaneous variability, determinations in an individual patient without multiple monitoring sessions are difficult. If a drug prevents arrhythmic symptoms that are closely correlated with heart disease, it may be thought of as effective. Other techniques that demonstrate the abolition of arrhythmias below 80% of a control level have also been advocated. More recently, the identification of agents that block the electrophysiologic induction of ventricular tachycardia has received widespread advocacy with the more highly refined electrophysiologic techniques. However, only a few agents prove to be effective by this means.

Third, there are some nonspecific approaches to determining efficacy. After therapeutic blood levels have been established, it is acceptable to administer the agent to produce an effective therapeutic blood level and to assume that efficacy has been achieved. It is also possible to establish the characteristics of a group of patients in a disease category by an analysis of variance, and the development of acceptable deviations from these established characteristics. Such a technique will be the subject of a report included in this symposium.

Included in the symposium are papers at the very forefront of our knowledge on arrhythmias, drugs for their treatment, and perspectives on future developments in this increasingly important field. We thank Merck Sharp & Dohme for their sponsorship of the meeting and their support for publishing this symposium.

The following abbreviations are used in the articles in this Symposium:

CAD = coronary artery disease
EF = ejection fraction
LV = left ventricular
MI = myocardial infarction
VF = ventricular fibrillation
VPC = ventricular premature complexes
VT = ventricular tachycardia

Importance of Metabolites in Antiarrhythmic Therapy

RAYMOND L. WOOSLEY, MD, PhD, and DAN M. RODEN, MD

The presence of metabolites with pharmacologic activity can produce unanticipated drug efficacy or toxicity. This is particularly true during treatment with drugs that have narrow therapeutic-toxic ratios, such as the antiarrhythmic agents. The presence of active metabolites can often be inferred from variability in the relation between pharmacologic effect and steady-state plasma concentrations of the parent drug. Moreover, metabolites may ordinarily be unimportant but can accumulate to therapeutic (or toxic) levels in disease states such as congestive heart failure, renal failure and hepatic failure. Further characterization of the contribution of such metabolites during treatment requires direct evaluation of their pharmacology in vitro, in animal models and, if indicated, in man. Procainamide and its active metabolite N-acetylprocainamide provide the best and most complete example of this sequence of observations. Other drugs, including quinidine, disopyramide, verapamil and the investigational agents encainide and lorcainide, have active metabolites for which pharmacologic activity is less well-defined. Further studies in this area will help reduce the frequency of antiarrhythmic drug adverse effects, make successful therapy more frequent, and perhaps allow insights into structure-activity relations.

(Am J Cardiol 1983;52:3C–7C).

Definition of the mechanisms of interindividual variability in drug response aims to improve therapeutics, that is, to decrease the occurrence of adverse effects and treatment failures. The selection of a drug dosage that maximizes therapeutic effects while minimizing adverse effects is particularly important for agents with low ratios between these endpoints. This requirement has provided the impetus for monitoring plasma drug concentrations in an effort to minimize interindividual variability in drug response due to differences in absorption, distribution or elimination. However, even under circumstances that produce comparable plasma drug concentrations, variability in response is still observed. There are a number of potential explanations for failure of plasma steady-state drug concentrations to correlate with pharmacologic effects, including assay nonspecificity, mediation of drug effects by the generation of ≥1 active metabolites, persistence of drug-induced cellular alterations after drug elimination has occurred, and the presence of drug in a "deep" effector site not detected by conventional pharmacokinetic analysis.[1] The formation of pharmacologically active metabolites is particularly relevant for the antiarrhythmic drugs, with their narrow therapeutic ratios, and is known to occur frequently.

From the Vanderbilt University School of Medicine, Nashville, Tennessee. This study was supported in part by Grants GM31304 and GM15431 from the United States Public Health Service. Dr. Roden is a recipient of the Clinical Scientist Award of the American Heart Association.

To individualize therapy and optimally monitor response, one must know the relative pharmacologic effects and potencies of a drug and its metabolites. During administration of the parent compound, the activity of metabolites can only be inferred, whereas direct comparisons of parent compounds and metabolites can be made in animal models. The final determination of pharmacologic activity of metabolites in man requires administration of the metabolites to patients. As outlined below, each of these approaches has been useful in the evaluation of antiarrhythmic drug metabolites.

Procainamide/N-Acetylprocainamide Studies

The rate of formation of N-acetylprocainamide, the major metabolite of procainamide, is influenced by a genetically determined pathway, N-acetylation. Because slow acetylators develop antinuclear antibodies and the lupus syndrome earlier in therapy than rapid acetylators,[2] this pathway can be viewed as relatively protective against lupus. Because antiarrhythmic activity was observed in patients with renal failure who accumulated much higher levels of N-acetylprocainamide than procainamide,[3] the hypothesis was advanced that N-acetylprocainamide might be an effective antiarrhythmic agent and that it might have the advantage of not inducing the lupus syndrome.[4] The next step in these studies was to compare the clinical pharmacologic properties of procainamide and N-acetylprocainamide in patients with ventricular arrhythmias.[5] N-acetyl-

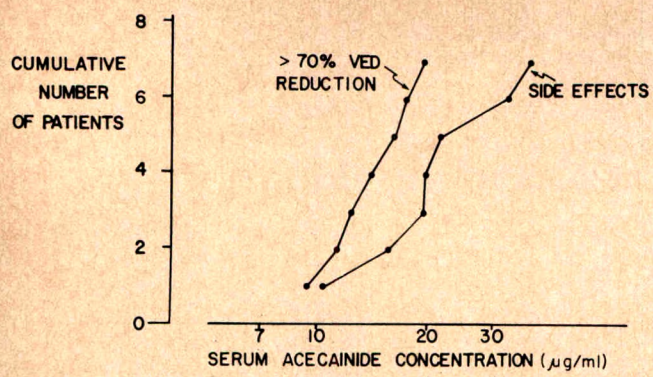

FIGURE 1. Relation between plasma concentration in N-acetylprocainamide (acecainide) and the occurrence of arrhythmia suppression and adverse effects. VED = ventricular ectopic depolarization. Reproduced from Roden et al[5] with permission of the publisher.

		PROCAINAMIDE	
		Sensitive	Resistant
ACECAINIDE	Sensitive	3	4
	Resistant	11	4
			p > 0.3

FIGURE 2. Comparison of response to procainamide and N-acetylprocainamide. Reproduced from Roden et al[5] with permission of the publisher.

procainamide was found to be antiarrhythmic in a minority of patients, but frequently produced adverse effects that limited therapy. Plasma concentrations associated with antiarrhythmic efficacy and the occurrence of adverse effects are shown in Figure 1. Individual responses to procainamide after intravenous administration (before appreciable N-acetylprocainamide was produced) was compared with subsequent responses to a series of oral doses of N-acetylprocainamide. In keeping with their reported different electrophysiologic characteristics,[6] response to one agent was not predictive of response to the other (Fig. 2). Furthermore, in patients treated on a long-term basis with N-acetylprocainamide, antinuclear antibodies and the lupus syndrome did not occur.[5,7–9]

These data have been valuable in monitoring the contribution of N-acetylprocainamide to the pharmacologic effects seen during long-term procainamide therapy. Few patients, with the exception of those with renal dysfunction, have accumulation of N-acetylprocainamide to concentrations that might contribute to antiarrhythmic efficacy. On the other hand, toxic effects of N-acetylprocainamide may explain the occurrence of gastrointestinal adverse effects in some patients who receive procainamide. Most importantly, this series of studies illustrates the way in which the presence of an active drug metabolite may be deduced by indirect means after administration of the parent drug and its activity may be confirmed and characterized by giving the metabolite itself to patients.

Studies with Metabolism of Encainide

During the investigation of new antiarrhythmic drugs, elucidation of the relation between the concentration of drug in plasma and its pharmacologic actions can lead to early detection of active metabolites. This was well demonstrated during the evaluation of the antiarrhythmic, electrocardiographic and dose-response effects of the very potent procainamide analog encainide.[10] Patients with total abolition of ventricular ectopy and ventricular tachycardia had rapid encainide elimination (half-life of 2 to 4 hours), marked electrocardiographic effects at variable dosages (12.5 to 75 mg every 6 hours), and highly variable (but low, 1 to 60 ng/ml) plasma concentrations of encainide. In contrast, in early studies a single nonresponding patient had much slower encainide elimination (half-life of 7.8 hours), higher plasma encainide concentrations, and yet no antiarrhythmic or electrocardiographic effects at dosages up to 125 mg every 6 hours. Chromatographic analysis of plasma from the responding patients revealed that the O-demethyl metabolite of encainide was present in greater quantities than the parent drug (Fig. 3); yet in the nonresponder it was hardly detectable except at very high dosages of encainide. The highly variable relation between plasma encainide and effects and these pharmacokinetic data therefore strongly suggested O-demethyl encainide might be active. Subsequent studies in a larger number of patients revealed that 6 to 10% of patients appear to lack the ability to rapidly form O-demethylate encainide[11]; in this group, encainide accumulates to high plasma concentrations[12] (Fig. 4).

In the initial clinical studies,[10] the only patient who failed to respond to encainide therapy was also the only patient who failed to form significant quantities of O-demethyl encainide. While this observation was a major clue to the existence of this active metabolite, the conclusion that encainide itself was inactive has not been supported by further observations. First, rapid intravenous infusion of encainide produces plasma concentrations much higher than those seen during long-term administration of oral encainide (in the absence of any metabolites) and antiarrhythmic responses have been repeatedly documented in this setting.[12–14] Second, in the subset of the patients who are genetically incapable of rapidly forming O-demethyl encainide (estimated at 6 to 10% of the population[11]), encainide itself accumulates to these high plasma concentrations. In these patients, antiarrhythmic response has been reported during long-term oral encainide therapy at usual encainide doses (25 to 50 mg 3 or 4 times daily). Also, in a study comparing encainide and quinidine,[15] trough encainide plasma concentrations were <60 ng/ml in 17 of the 20 patients and concentrations of 200, 360 and 1,140 ng/ml were recorded at trough in 3. Therefore,

these subjects were probably metabolizing encainide poorly and lacked significant quantities of O-demethyl encainide in plasma. Two of the 3 patients were encainide responders, 1 at 25 mg every 6 hours and 1 at 50 mg every 6 hours; the third patient had 65% suppression of ventricular ectopic depolarizations. Therefore, poor metabolizers can respond to encainide and do so at usual dosages because they accumulate higher levels of the less potent parent compound.

The genetic variability in capacity to metabolize encainide has been used to evaluate the relative potency of encainide and its metabolites.[12] By administering an acute intravenous infusion of encainide to patients with ventricular arrhythmias, the pharmacologic effects of encainide could be determined before substantial quantities of metabolites could accumulate in plasma, especially in 2 patients with slow O-demethylation. An antiarrhythmic effect attributable to encainide itself was only seen when its plasma concentrations reached high levels (range 250 to 1,000 ng/ml). However, during long-term oral therapy in extensive O-demethylators, there was a good correlation between plasma O-demethyl encainide (usually 50 to 300 ng/ml) and effect.[12]

The pharmacologic properties of this metabolite have been directly evaluated in vitro[16] and in vivo[17,18] and it has been found to be 5- to 50-fold more active than the parent drug. Because its plasma concentrations usually exceed those of the parent encainide, it appears likely that it mediates most of the effects seen during encainide therapy in rapid O-demethylators. Some reported toxicity during encainide therapy may have been a result of rapid dose escalation, with the result that plasma concentrations of active metabolites (with apparently longer half-lives than encainide) accumulated into a toxic range.[19] Further evaluation of the pharmacologic properties of encainide metabolites in man awaits their direct administration to patients.

Studies with Quinidine and Metabolites

Metabolites of other antiarrhythmic agents may be active but few studies have shown direct and convincing evidence of pharmacologic effects in man. By comparing the effects of intravenous and oral quinidine in normal subjects, Holford et al[20] concluded that pharmacologically active metabolites caused a greater QTc prolongation after oral administration. This was the first convincing evidence that the metabolites of quinidine might be pharmacologically active in man, but the investigators could not assess the potential antiarrhythmic efficacy of the metabolites.

It has been asserted that the correlation between plasma quinidine concentration and antiarrhythmic

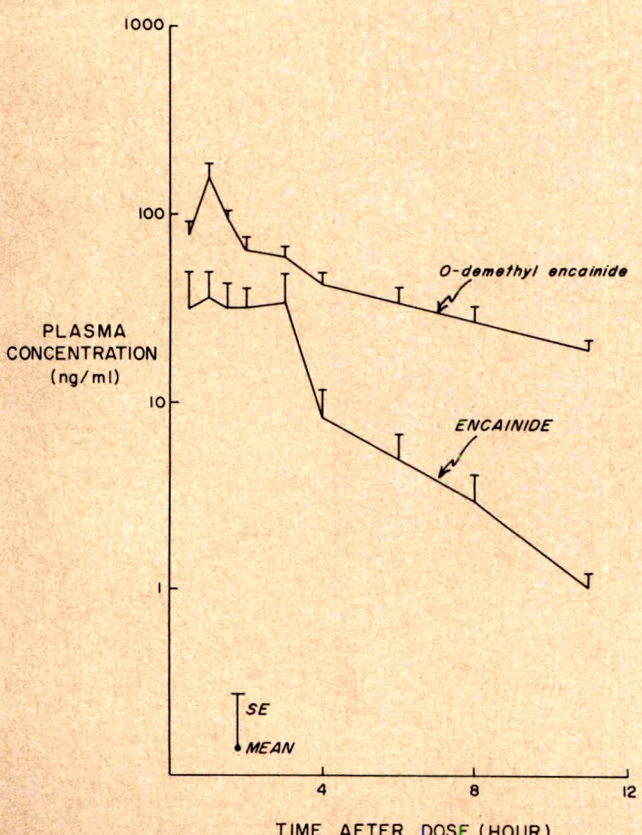

FIGURE 3. Plasma concentration of encainide and O-demethyl encainide after a 25-mg oral dose of encainide in patients who responded to encainide therapy. SE = standard error.

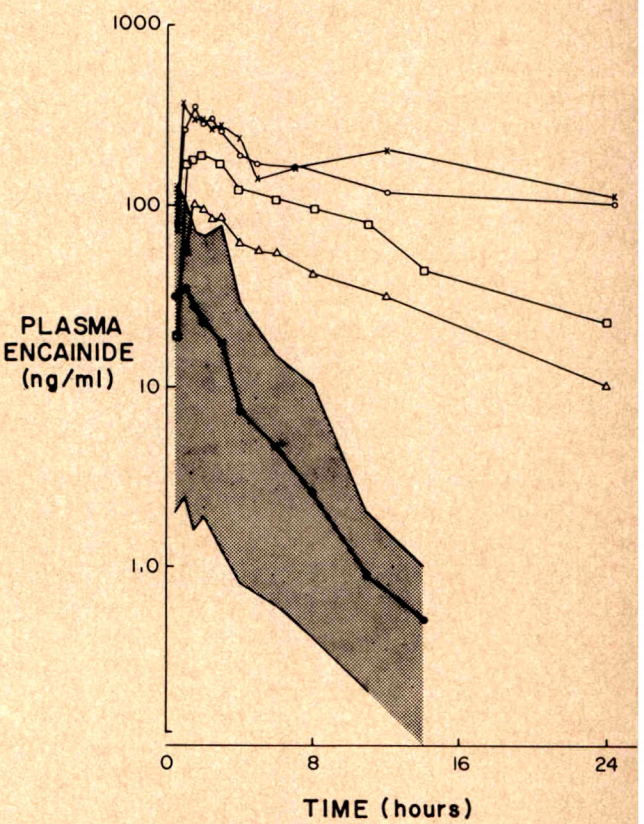

FIGURE 4. Plasma encainide concentration after a 25-mg oral dose of encainide. The upper 4 curves are from subjects with very slow elimination and no detectable O-demethyl encainide in plasma. O-demethyl encainide was seen in higher concentrations than encainide in the remaining subjects, whose mean data are shown by the **shaded area** (n = 15).

efficacy (conversion of atrial fibrillation) described by Sokolow and Edgar in 1950[21] was found only because the assay used was nonspecific and measured metabolites that contributed to pharmacologic activity.[22] Accordingly, the subsequently developed assays based on either double organic extraction,[23] enzyme immunoassay[24] or, more recently, high-performance liquid chromatography[25,26] are each more specific and therefore yield successively lower values when patient samples are assayed for "quinidine."[22,24] However, the relation between the more specific "plasma concentration" and antiarrhythmic efficacy has not been well defined. In addition to the indirect evidence in normal volunteers,[20] animal studies have been performed that suggest that some quinidine metabolites are active[27,28]; in one study, the major metabolite 3-hydroxy-quinidine actually exacerbated test arrhythmias.[28] As with procainamide and encainide, the rate of formation of this active quinidine metabolite appears to be highly variable.[29] Therefore, if the metabolites of quinidine do contribute to the effects seen in man, the newer assays may actually be less useful in monitoring therapy. Of equal importance, the newer assays (double organic extraction and enzyme immunoassay) might fail to measure metabolites that could accumulate to toxic concentrations.

Beta Blockers and Metabolites

Recent evidence has indicated the importance of active metabolites during beta-blocker therapy. Several metabolites of propranolol have been identified. One, 4-hydroxypropranolol, is formed principally after oral administration and appears to have beta-blocking properties.[30] Any interaction with propranolol itself is speculative. Another metabolite, the glucuronide, is itself not active but can be converted back to propranolol and may thus explain persistence of measurable propranolol plasma concentration days after stopping therapy.[31] Newer beta-blocking drugs (such as metoprolol and acebutolol) also have active metabolites; their contribution to the overall drug effect remains unknown. At least some of the variability in metoprolol metabolism is genetically determined, probably by the same gene that determines encainide metabolism.[32]

Metabolites of Other Antiarrhythmic Drugs

Lidocaine is de-ethylated in one pass through the liver to monoethylglycinexylidide and glycinexylidide. Using indirect techniques, it has been concluded that both have antiarrhythmic activity in man, but are less potent than the parent drug.[33,34] More importantly, monoethylglycinexylidide, like lidocaine, can produce seizures in animals, and addition of glycinexylidide to either appears to potentiate convulsant activity.[35] Unlike the parent drug, both metabolites are excreted in the urine. Monoethylglycinexylidide does not appear to accumulate in renal failure, probably because it is further de-ethylated to glycinexlidide. Although glycinexylidide may accumulate in renal failure, its overall contribution to the effects of lidocaine is probably small enough that no change in lidocaine dosing is required in renal disease. Lidocaine assay systems do not measure these metabolites.

Another antiarrhythmic agent, lorcainide, which has only recently been investigated in man, has a metabolite that appears to contribute significantly to antiarrhythmic and electrocardiographic effects during treatment.[36,37] In fact, the metabolite norlorcainide was administered to one patient and did suppress arrhythmias.[36] Disopyramide, verapamil and the investigational agents aprindine and amiodarone all have metabolites that may have antiarrhythmic activity. Mexiletine, tocainide and flecainide do not at this time appear to have active metabolites. However, the extent to which any metabolites accumulate in disease and the interactions between parent and metabolite have not been explored.[38] Should concentration monitoring in plasma become routine for these drugs, such data will be important.

Clinical Implications: Known and Potential

The presence of active metabolites of antiarrhythmic drugs can explain an unanticipated therapeutic effect such as arrhythmia suppression despite low plasma concentrations of procainamide in renal failure. An extremely variable relation between plasma drug concentration and effect should raise the possibility that active metabolites may be present (such as encainide). As outlined earlier, active metabolites of procainamide and perhaps many other drugs may also account for adverse effects during therapy. Also, some "idiosyncratic" adverse effects, such as agranulocytosis during aprindine therapy or quinidine-induced torsades de pointes, may be linked to genetically determined patterns of drug metabolism that are only now being explored. Further knowledge of the pharmacologic properties of active metabolites of antiarrhythmic drugs will help decrease the incidence of adverse effects and increase the frequency of successful therapy. Insights into the relation between structure and function in closely related compounds could allow the design of safer, more effective drugs.

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Plasma Level Monitoring of Antiarrhythmic Drugs

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It is widely accepted that the effects (both cardiac and extracardiac) of antiarrhythmic drugs are modulated by their concentration at some unidentified active site, and that the drug concentrations in the systemic circulation and at these active sites are in equilibrium. Thus, antiarrhythmic drug effects can be related directly to systemic plasma concentrations, and an optimal plasma concentration can be identified at which satisfactory arrhythmia suppression can be achieved in the absence of intolerable adverse effects. This optimal concentration is influenced by several factors that give rise to significant interpatient variability. These factors include serum protein binding, active metabolites, intrinsic responsiveness and myocardial accumulation.

Although plasma concentration guidelines have been suggested for most antiarrhythmic drugs, they are generally not statistically derived and, with the exception of procainamide, are extrapolated from small patient samples. They generally represent the experience of an investigator or group of investigators treating a small homogeneous patient population. Interpretation of plasma concentrations of antiarrhythmic drugs also requires consideration of pharmacokinetic factors. Plasma drug levels are only useful when dosing history and timing of the blood sample, relative to drug administration, are considered.

Despite several limitations, plasma concentration monitoring of antiarrhythmic drugs can be helpful if evaluated with an understanding of the pharmacokinetic properties of the drug being measured, the clinical status of the patient and an appreciation of the factors that may influence the relation between the measured level and resultant clinical response.

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Monitoring antiarryhythmic drug therapy by means of measuring blood or plasma concentrations dates back 40 years to the development of the first chemical method for measuring quinidine concentrations in human plasma.[1] After this report, several investigators evaluated the relation between the plasma concentration and cardiac effects of quinidine; in 1950, Sokolow and Edgar,[2] in an extensive report, described the clinical pharmacology of quinidine, and then proposed, for the first time, plasma concentration guidelines for an antiarrhythmic agent.

More than 20 drugs are either available for clinical use or are undergoing evaluation as antiarrhythmic agents. Analytic methods exist for measuring the plasma concentrations of most of these drugs, and an extensive literature has accumulated regarding their clinical pharmacology. Numerous studies that describe the disposition kinetics and the plasma level–effect relations of these drugs have been reported.

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It is now widely accepted that the effects (both cardiac and extracardiac) of antiarrhythmic drugs are modulated by their concentration at an unidentified active cellular site and that the concentrations in the systemic circulation and these active sites are in equilibrium. Thus, antiarrhythmic drug effects can be related directly to systemic plasma concentrations. Therefore, an optimal plasma concentration can be identified at which satisfactory arrhythmia suppression can be achieved in the absence of intolerable adverse effects. This optimal concentration is influenced by several factors, which gives rise to significant interpatient variability. The result of this variability is a range of therapeutic plasma concentrations. While these "therapeutic concentration ranges" are not always fully defined, they are useful because the plasma concentration-response relation is far more predictable than the relation between the dose and response.

The intent of this report is to summarize the state of knowledge that relates to the use of measured plasma levels of antiarrhythmic drugs and to discuss factors that modulate the relation between their measured plasma concentrations and cardiac effects.

TABLE I Degree of Serum Protein Binding of Antiarrhythmic Drugs

Drug	% Bound
Aprindine	90
Bretylium	6 ± 3.7*
Disopyramide	40–90†
Encainide	90
Lidocaine	25–50†
Lorcainide	85 ± 5*
Phenytoin	93.7 ± 0.4*
Procainamide	15–20
Propafenone	97
Quinidine	60–90
Tocainide	50
Verapamil	89.6 ± 0.17*

* Values are mean ± standard deviation.
† Concentration-dependent.

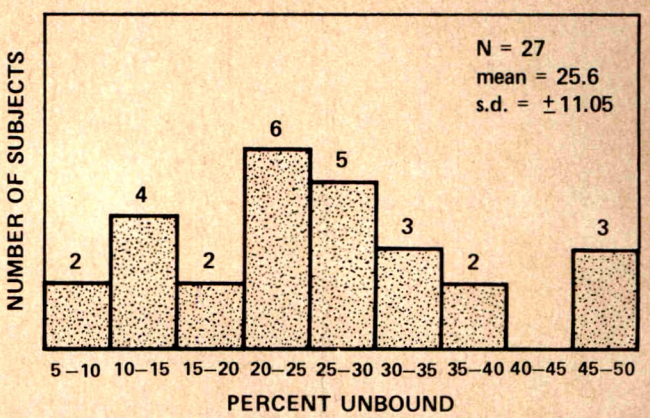

FIGURE 1. Degree of serum protein binding of quinidine in 27 patients. The total serum concentration in all samples was about 2 g/ml. Reproduced from: Kates RE. Therapeutic monitoring of antiarrhythmic drugs. Ther Drug Monit 1980;2:119–126, with permission of the publisher.

Factors That Influence the Plasma Level–Effect Relation

Protein binding: Much has been written about the role of plasma protein binding of drugs and the role it plays in moderating the plasma level–effect relationship.[3,4] The accepted view is that only free drug molecules (not bound to plasma proteins) in the plasma equilibrate with drug at the active site in the myocardium because only free drug molecules can cross cell membranes. Thus, only unbound drug is available to produce an antiarrhythmic effect. All antiarrhythmic drugs bind to plasma proteins, and several are highly bound (Table I). In most cases this binding is relatively constant from patient to patient, but for a few drugs there is considerable interpatient variability. Also, the extent of binding of most drugs is independent of the total plasma concentration. Lidocaine and disopyramide are exceptions to this rule in that their binding decreases with increasing total plasma levels due to saturation of the protein binding sites. Some of the variability in response to antiarrhythmic drugs may be due to differences in the extent of plasma protein binding. For highly bound drugs, small changes in the extent of binding can make significant differences in the effective free concentration and, possibly, activity.

In almost all cases the actual measured plasma concentrations of antiarrhythmic drugs represent total (bound plus free) drug in the plasma. The evaluation of the degree of protein binding can be determined by means of equilibrium dialysis, ultrafiltration or ultracentrifugation. Although these are viable procedures in a research environment, they are too time-consuming and costly to be performed as a routine clinical laboratory procedure. Although one does not usually have binding data available for an individual patient, it is necessary to keep in mind that variability in binding translates into variability in free concentration, which affects the relation between the total plasma concentration and the effect. An example of interpatient variability is shown in Figure 1, which is a summary of quinidine protein binding data from 27 patients. The total measured plasma concentration of quinidine in each patient sample was approximately 2 μg/ml, and there was no significant difference in the total serum protein or albumin concentration in these samples. These data show that the interpatient variability in quinidine binding is substantial, with a range of 5 to 50% for unbound drug. The actual free plasma concentration of quinidine varied from 0.1 μg/ml in patients with only 5% free to 1 μg/ml in those with 50% free. The free concentrations varied by a factor of 10, even though all patients had the same measured total plasma concentration of quinidine. In considering protein binding data, such as presented in Table I, the magnitude of the range is at least as important as the average value. When a patient has signs of toxicity or is nonresponsive to an antiarrhythmic drug despite measured total plasma levels within the generally accepted therapeutic range, a factor that should be considered is the plasma protein binding.

In addition to interpatient variability in plasma protein binding, intrapatient variability can contribute to the difficulty of interpreting total plasma drug concentrations. Intrapatient variability can be due to physiologic changes, drug interactions, concentration-dependent saturable binding, or physiologic variation in the disease process. Routledge et al[5] reported changes in lidocaine binding in patients after acute myocardial infarction. After an infarction, plasma concentrations of alpha$_1$-acid glycoprotein, a protein to which lidocaine binds, increase with time. The protein binding of lidocaine increases, with a subsequent reduction in free fraction. Their study demonstrated a statistically significant change in lidocaine binding with time in post-infarction patients; however, the clinical significance remains to be further documented.

Concentration-dependent binding has been reported for 2 antiarrhythmic drugs—disopyramide and lidocaine. This phenomenon not only confuses the interpretation of measured drug concentrations, but greatly increases the complexity of titrating patients to an optimal dose. The concentration-dependence of the plasma protein binding of disopyramide in 2 patients reported by Meffin et al[6] is shown in Figure 2. The free fraction increases dramatically for both patients over

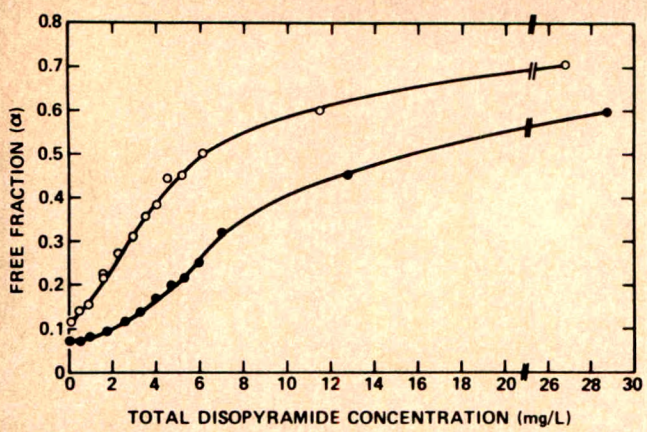

FIGURE 2. Free fraction of disopyramide in the plasma versus the total plasma concentration. Patients 11 (**open circles**) and 12 (**solid circles**) from Meffin et al.[6] Reproduced from Meffin et al[6] with permission of the publisher.

TABLE II Metabolites of Antiarrhythmic Drugs

Drug	Major Metabolites	Relative Potency	Relative Plasma Concentration
Amiodarone	N-desethylamiodarone	...	1
Aprindine	N-desethylaprindine	1	0.2
Disopyramide	N-desisopropyl-diso-pyramide	<0.5	0.5
Encainide	O-demethylencainide	>1	5
	3-methoxy-O-demethyl-encainide	≥1	5
Lidocaine	Monoethylglycine xylidide	0.83	0.5–2
	Glycine xylidide	0.1	0.1–1
Lorcainide	Norlorcainide	1	0.5–4
Procainamide	N-acetylprocainamide	<1	0.5–2.5
Quinidine	3-hydroxyquinidine	1	0.2–0.8
Verapamil	Norverapamil	0.25*	1

* The potency of norverapamil relates to its vasodilatory properties; its effects on cardiac conduction have not been reported.

the range of generally observed therapeutic levels (3 to 6 μg/ml). As the total plasma concentration of disopyramide increases from 1 to 6 μg/ml in Patient 11, the free fraction increases from 0.175 to 0.49. The consequence of an increase in total disopyramide concentration from 2 to 4 μg/ml is an increase in the actual free concentration by a factor of 4. Thus, small changes in the total plasma concentration can produce significantly larger changes in the actual free (active) concentration. Subsequently, a much greater response than anticipated based on the total plasma level might occur. Such a situation suggests a need for caution when titrating a drug with nonlinear binding. Similar data have been reported for lidocaine.[7] As the total plasma concentration of lidocaine is increased through the therapeutic range from 1 to 6 μg/ml, the free concentration increases from about 25 to 50% of the total. Since lidocaine is not highly bound in the plasma, this change in extent of binding does not represent as significant a concern as with disopyramide.

Active metabolites: Most antiarrhythmic drugs are extensively metabolized.[8] In some cases, the metabolites produced are cardioactive and accumulate extensively. Active metabolites of some antiarrhythmic drugs may be of equal or greater potency than their parent drug, or may even produce effects that are qualitatively different. In some cases, metabolites may produce noncardiac adverse effects that limit the clinical value of the parent drug. Listed in Table II are the major metabolites of several antiarrhythmic drugs. These metabolites either have been reported to accumulate in plasma of patients after administration of the parent drug or have been reported to be pharmacologically active. Some of these metabolites meet both criteria, are cardioactive and accumulate extensively. Evaluations of activity of antiarrhythmic drug metabolites are generally conducted in animal arrhythmia models, and only rarely have metabolites been studied after direct administration to patients. However, from knowledge of antiarrhythmic activity in animals and of the degree to which a metabolite accumulates in the plasma of patients, qualitative judgments can be made about its therapeutic role. Such judgments, however, must be recognized as tenuous. Quantitative judgments require further information regarding the relation between the parent drug and the metabolites when present simultaneously in the myocardium. One must consider whether the effects of the parent drug and metabolite are additive, synergistic or even antagonistic. The latter case is most likely with drug-metabolite pairs in which the metabolite accumulates substantially but does not have significant antiarrhythmic potency.

The role of metabolites also must be considered with regard to differences in the disposition kinetics between a parent drug and metabolite. As has been demonstrated by the metabolites of lorcainide[9] and encainide,[10] the time course of accumulation and disappearance of a metabolite may be much different from that of the parent drug. Norlorcainide and the active metabolites of encainide have much longer half-lives and smaller distribution volumes than their parent drugs. While steady-state plasma levels of encainide and lorcainide are achieved rapidly, it requires several days to weeks before their metabolites have accumulated to their steady-state levels. Figure 3 illustrates the difference in disposition characteristics of encainide and its 2 active metabolites. These data were obtained during a washout phase of a long-term oral dosing study.[10] The disappearance half-lives of the 2 metabolites are considerably longer than that of the parent drug. Clinical assessment, as well as interpretation of a measured plasma concentration, must take into account the time required to achieve steady-state concentrations of the relevant metabolites as well.

The n-acetyl metabolite of procainamide (NAPA) has received considerable attention over the past years,[11,12] and much confusion has arisen regarding the interpretation of simultaneously measured procainamide and NAPA levels. Procainamide and NAPA are qualitatively and quantitatively different in their effects on cardiac conduction.[13,14] Unless NAPA accumulates to plasma levels greater than about 15 μg/ml in patients who are taking procainamide, its accumulation is of

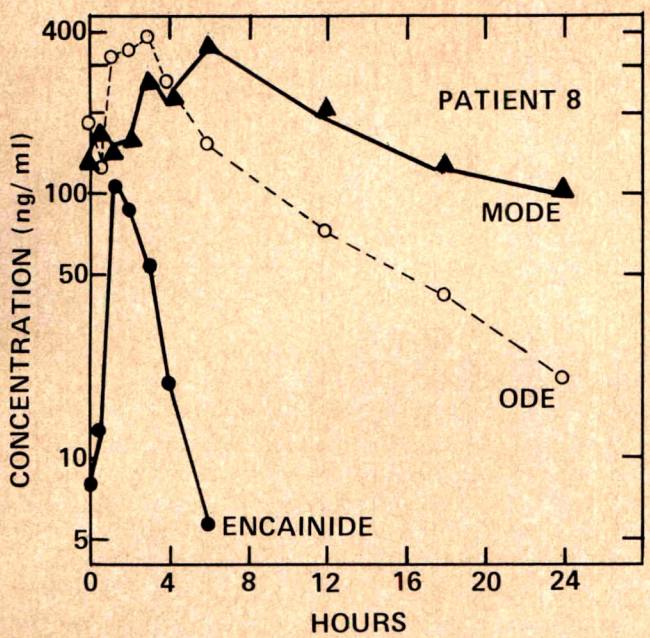

FIGURE 3. Plasma concentration-time curves for encainide (**closed circles**), O-demethyl encainide (ODE) (**solid circles**) and 3-methoxy-O-demethyl encainide (MODE) (**triangles**) in a patient after discontinuation of long-term oral encainide therapy. Reproduced from Kates et al[10] with permission of the publisher.

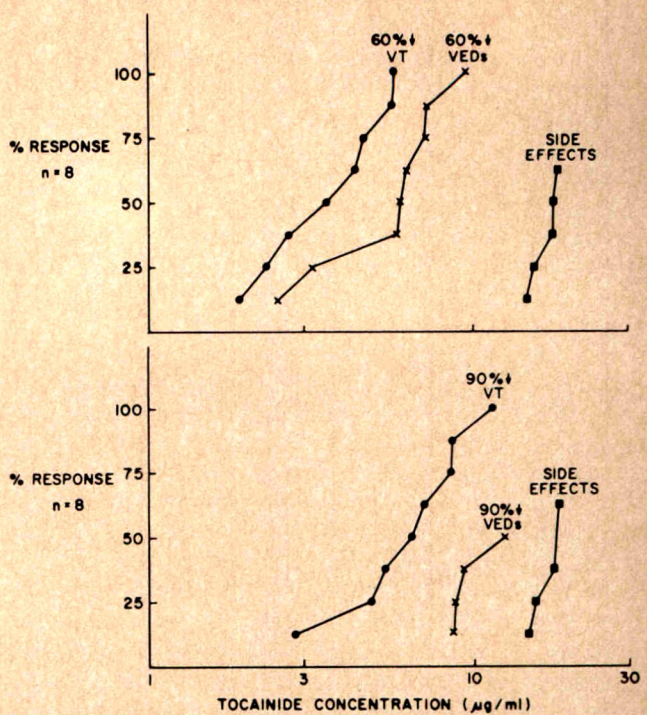

FIGURE 4. Dose-response relationships for suppression of ventricular ectopic depolarizations (VED), ventricular tachycardia (VT) and side effects for 8 patients with frequent VT. Reproduced from Roden et al[16] with permission of the publisher.

little consequence. However, the accumulation of NAPA to levels >15 μg/ml due to renal failure or other causes confounds the interpretation of measured procainamide plasma levels. As with other parent drug–metabolite combinations, no good guidelines exist for evaluating their combined effect, and caution must be exercised.

Most analytic methods used in clinical drug assay facilities measure only the unchanged parent drug. The presence of >1 active species (parent drug plus metabolites) clearly confounds the interpretation of a measured drug level.

Intrinsic responsiveness: In addition to the concentration of drug at some active site in the myocardium, the clinical effectiveness of an antiarrhythmic drug also depends on the responsiveness of this target tissue. Factors that influence responsiveness include type of arrhythmia, other concurrent physiologic abnormalities, environmental factors, genetic influences and, in some cases, previous drug therapy.

Connolly et al[15] reported that repetitive ventricular activity is suppressed at plasma drug concentrations lower than those required to suppress isolated ventricular premature beats. Roden et al[16] evaluated the clinical efficacy of tocainide in patients with symptomatic ventricular arrhythmias and related arrhythmia suppression to plasma tocainide levels. They found that tocainide suppressed ventricular tachycardia to a greater extent than isolated ventricular ectopy at all concentrations and that increases in plasma levels produced progressive suppression of both. Their data demonstrated parallel, but distinctly different, plasma level–response relations for repetitive and single forms of ventricular ectopy (Fig. 4).

We recently observed similar differential effects with propafenone.[15] The relation between arrhythmia suppression and plasma levels of propafenone was studied in patients with histories of frequent ventricular premature contractions. Repetitive ventricular activity was suppressed at plasma concentrations lower than those required to suppress isolated extra beats.

Although the plasma level–effect relation for single and repetitive forms of ventricular ectopy are different, they do overlap the same concentration range, and the differences are probably not clinically important. These observations do, however, suggest that different mechanisms may be responsible for single and repetitive forms of ventricular ectopy. These differences in plasma levels associated with suppression of isolated and repetitive ventricular ectopy suggest the need to consider the arrhythmia being suppressed when "therapeutic levels" are being defined. Furthermore, it is clear that the relation between plasma drug levels and the prevention of ventricular fibrillation is unknown.

In addition to arrhythmia sensitivity, other physiologic factors have been shown to influence responsiveness to drug therapy. As pointed out by Koch-Weser,[17] hypokalemia, hypercalcemia, hypomagnesemia, acid-base disturbances, increased adrenergic tone, hypothyroidism, hypoxemia, myocardial ischemia and severe cardiac failure all can influence the response to digoxin therapy.

Myocardial uptake: The cellular site of action of antiarrhythmic drugs is not known. However, it has

been assumed for years that a receptor, or membrane binding site, is involved in the action of drugs that affect cardiac conduction. The argument that free (non–protein-bound) drug in the plasma is a good measure of the concentration of "active" drug at the receptor site rests on the hypothesis that a reversible interaction occurs between free drug and a binding site, as described by classic enzyme kinetics. It has been argued that myocardial binding of antiarrhythmic drugs is primarily to inactive sites[17] and that free plasma levels better reflect the "active" drug concentration in the myocardium. This generally accepted assumption, however, deserves closer evaluation.

Anderson et al[18] have studied the time course of action of bretylium in a dog model, and reported that the time course of action of this drug correlates better with the time course of uptake and disposition of drug in the myocardium than with plasma concentrations. After a single intravenous bolus dose of bretylium, the maximal effect was not observed until 6 hours after administration, despite the significant decrease in plasma concentrations over this time period. They observed, however, that myocardial tissue levels of this drug increased over this time period, reaching a maximal level around 6 hours. They attributed this slow onset of action to the delay in myocardial uptake. A similar finding was reported for amiodarone.[19] The delay in uptake of amiodarone into the myocardium of anesthetized dogs also was shown to correspond with the delay in onset of effect. These 2 drugs demonstrate that myocardial tissue levels may be important determinants in modulating the effect of antiarrhythmic drugs. These 2 drugs are unique in that they are taken up slowly into the myocardium, and, at early times, plasma and myocardial levels are not changing in parallel. This allows a separate look at the relation between the plasma and the myocardial drug concentrations and effects.

Other studies in dogs have shown that considerable variability can exist in the myocardial/plasma concentration ratio[20,21] of antiarrhythmic drugs. Where myocardial tissue levels of antiarrhythmic drugs moderate their effects, this variability in myocardial/plasma concentration ratios may significantly contribute to variability in effective plasma concentrations.

When Is It Helpful to Measure Plasma Concentrations of Antiarrhythmic Drugs?

Numerous factors can influence the relation between the plasma concentration and the effect of antiarrhythmic drugs. Despite these concerns, plasma level monitoring of antiarrhythmic drugs can be useful. Plasma concentrations of antiarrhythmic drugs are especially helpful in guiding dosage adjustments when therapeutic endpoints are not readily measurable. The most obvious situation is prophylactic therapy to prevent recurrences of paroxysmal arrhythmias, including sudden death. In this situation, one has the option to adjust a dosage regimen to toxicity and then back off, or to adjust the dose to achieve plasma concentrations within established guidelines. The former is a viable approach in some environments in which close patient monitoring is possible, and early toxicity is neither life-threatening nor intolerably severe. However, the use of plasma level monitoring to adjust dosage is generally safer, simple and inexpensive. Plasma level guidelines, as used in this situation, are imperfect but do provide a reasonable basis for dosage adjustment in the absence of other quantifiable endpoints.

Another important use of plasma level monitoring of antiarrhythmic drugs is in the evaluation of therapeutic failures. Failure to suppress symptomatic or otherwise detectable arrhythmias with reasonable or high drug doses can be due to "true therapeutic failure," to bioavailability or pharmacokinetic factors or to poor patient compliance. As mentioned earlier in this report, the relation between administered dose and effect is far less predictable than the plasma level–effect relation. A major factor that influences the dose-response relation is bioavailability. Due either to poor absorption or high hepatic extraction, an administered dose may not reach the systemic circulation in sufficient amounts to produce effective concentrations at the active site. The only way to differentiate this problem from a true therapeutic failure is to evaluate the drug concentration in the blood. Bioavailability deficiencies can be overcome by dosage adjustments, whereas true therapeutic failures require changing to another drug.

Plasma concentration monitoring of antiarrhythmic drugs is also useful when their absorption or disposition is altered by pathophysiologic changes. Benowitz and Meister[22] reviewed the effects of cardiac failure on the pharmacokinetic properties of several drugs. They pointed out that cardiac failure is frequently associated with alterations in cardiac output, autonomic tone, central and systemic venous pressure, tissue hypoxia, visceral congestion and gastrointestinal motility. Cardiac failure significantly alters the dispostion kinetics of both quinidine[23] and lidocaine.[24] In both cases the clearance is reduced and the distribution volumes are less than normal. The consequence of these changes is higher plasma levels for a given dosage regimen. Although the direction of this alteration is predictable, considerable variability exists in the degree of these changes. Thus, monitoring plasma levels is extremely helpful.

Other situations in which plasma level monitoring of antiarrhythmic drugs is useful are emergency admissions, treatment of patients with impaired renal or hepatic function, and those in which concurrent administration of interacting drugs is necessary.

Pharmacokinetic Factors

Plasma drug levels can be interpreted only when dosing history and timing of the sample, relative to a prior dose, are considered. During long-term oral drug administration, it is generally recommended that blood be drawn near the end of the dosage interval so that the measured concentration represents the minimal or trough level. Within a dosage interval, levels can change dramatically, especially for rapidly eliminated drugs. At the very least, it is necessary to document the time a blood sample was drawn relative to the prior dose.

TABLE III Plasma Level Guidelines for Antiarrhythmic Drugs

Drug	Plasma Level Range (μg/ml)
Amiodarone	0.5–2
Aprindine	1–2
Bretylium	0.8–2.4
Disopyramide	3–6
Lidocaine	1.4–6
Lorcainide/norlorcainide	0.04–0.2/0.08–0.3
Mexiletine	0.75–2
Phenytoin	10–18
Procainamide	4–8
Quinidine	2–5
Tocainide	6–15

It is also important to consider how long a patient has been taking a particular drug and whether there has been any recent change in the dosage regimen. Although the interpretation of a measured plasma concentration does not necessitate that a steady state be achieved before drawing a blood sample, it is useful to know if a steady state has been achieved or if further accumulation can be anticipated with the current regimen. A time period equivalent to about 5 times the half-life of a drug is necessary to achieve steady-state. This principle applies whether one is initiating therapy with a new drug or simply changing the dose or dosing frequency. As stated earlier, metabolites may have longer half-lives than their parent drug. Their time of accumulation also must be considered, especially if they are cardioactive.

Therapeutic Ranges

The concept of a therapeutic range is best illustrated by the report of Koch-Weser and Klein[25] in which they relate clinical status to plasma concentrations of procainamide for 146 patients who were treated for cardiac arrhythmias. Their data demonstrated a normal distribution of plasma concentrations associated with clinical efficacy. They identified a lower level, below which the probability of a therapeutic response was low, and an upper limit, above which the probability of toxicity was significant. Although they demonstrated a broad range of plasma levels over which arrhythmia suppression was achieved, most patients responded within the range of 4 to 8 μg/ml. "Therapeutic plasma concentration ranges" have been suggested for most antiarrhythmic drugs (Table III). The title "therapeutic range" is a misnomer and probably generates greater expections than are justified. A more appropriate title would be "plasma level guidelines." Whereas the therapeutic range for procainamide is based on a large patient sample, with a sufficient occurrence of level-related toxic side effects, this is not the case for most other antiarrhythmic drugs. These ranges are not statistically derived and, with the exception of procainamide, are obtained from small patient samples. They generally represent the experience of an investigator or group of investigators treating a small homogeneous patient population. These ranges are not rigorous and, in most cases, must be extensively refined by the evaluation of larger numbers of patients. The plasma levels associated with increasing likelihood of level-related toxicity need to be defined more carefully for almost all antiarrhythmic drugs.

Conclusions

Plasma concentration guidelines have been proposed for most antiarrhythmic drugs. The relation between measured plasma concentration and effect is not well characterized for most drugs, and it is recognized that it is influenced by several variables. Despite several limitations, plasma concentration monitoring of antiarrhythmic drugs can be helpful if evaluated with an understanding of the pharmacokinetic properties of the drug being measured and the clinical status of the patient being treated.

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Hemodynamic Effects of Antiarrhythmic Drugs

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In order to use antiarrhythmic drugs safely, one must understand their hemodynamic effects. Quinidine and the calcium antagonists have direct cardiac effects and frequently opposing autonomically mediated or indirect cardiac effects. Lidocaine is exceptionally well tolerated, even by patients with severe left ventricular dysfunction. Phenytoin and procainamide have the potential for serious adverse effects, but are generally well tolerated at usual doses. Disopyramide causes serious depression of left ventricular function in many patients because of its direct myocardial depressant and peripheral vasoconstricting actions. Although bretylium causes an immediate increase in contractility, it can ultimately result in important hypotension. In this review the in vitro and in vivo hemodynamic effects of these and other antiarrhythmic drugs are discussed to provide information that will assist the clinician in using these drugs properly.

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Patients with coronary artery disease, cardiomyopathy or significant valvular heart disease often have symptomatic or life-threatening arrhythmias that require short- or long-term drug therapy. In these patients, many of whom have a marginally compensated cardiovascular system, one must be concerned about a drug's cardiac and peripheral vascular effects. A small further decrease in myocardial contractility or a change in peripheral vascular resistance may mean the difference between compensated congestive heart failure and pulmonary edema or the difference between borderline low blood pressure and symptomatic hypotension or shock. It is important to understand all of the cardiovascular effects of any antiarrhythmic medication in order to choose the most appropriate agent for any clinical setting.

For these reasons, we review the hemodynamic effects of the frequently used antiarrhythmic agents. Although for many drugs discussed we describe the findings of relevant in vitro and in vivo animal experiments, the major emphasis is on studies that are most applicable to the care of the patients with heart disease. We focus on the drugs that are often prescribed, with less emphasis on medications that are still under investigation and are not yet available for widespread use.

A review of the hemodynamic effects of antiarrhythmic drugs shows a variety of contradictory results. A drug that has a negative inotropic effect in one setting will be shown to increase cardiac output in another. Frequently, the methods used for evaluation can explain these differences. Distinguishing the primary from the secondary effects of an antiarrhythmic drug is important because many of the drugs have a direct effect on the myocardium that is offset by a peripheral or adrenergic effect (Table I). Similarly, direct effects of an agent may be balanced by autonomic reflex actions in response to those or other direct actions. Depending on the balance, overall effects can vary greatly. These interactions can often explain the differing results of studies of isolated myocardial tissue versus those of studies of an intact organism. They can also explain differences between animals with their autonomic reflexes altered, either pharmacologically or surgically, and those that have not been so treated. Other, more obvious factors explaining these differences relate to variation in dose and rate of administration of a drug, nonuniform effects from species to species, and the difficulty in extrapolating these to man, and the differences between anesthetized and unanesthetized subjects. Finally, a distinction must be made between statistically significant and clinically significant results. Some minor hemodynamic effects of an antiarrhythmic drug detected by sensitive methods may reach statistical significance, but have little clinical relevance.

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Quinidine

Recognizing the primary and secondary cardiovascular effects of quinidine is difficult. Some studies of isolated cardiac muscle have shown quinidine to reduce contractile force;[1–3] others have shown a slight increase in contractility,[4] and one showed a positive or negative effect, depending on the quinidine concentration and the rate of electrical stimulation.[5] Overall, depression

TABLE I Summary of Hemodynamic Effects of Antiarrhythmic Drugs

Drug	Direct Effect on Myocardial Contractility	Effect on Peripheral Vascular Resistance	Usual Effect on Cardiac Output	Usual Effect on Blood Pressure
Quinidine				
IV	↓↓	↓↓↓	↓→↑	↓↓↓
PO	→↓	→↓	→	→↓
Procainamide				
IV	↓	↓↓	→	↓↓
PO	↓	↓	→	→
Lidocaine	→	→	→	→
Bretylium				
Early	↑	↑	↑	↑
Late	→	↓↓	→	↓↓↓
Disopyramide	↓↓↓	↑↑	↓↓↓	↑
Phenytoin	↓	↓	→	↓
Diltiazem	↓	↓	→↑	↓
Verapamil	↓↓	↓↓	↓→↑	↓↓
Amiodarone	↓	↓	↓→↑	↓
Mexiletine	→	→	→	→
Tocainide	→	↑	→	→
Encainide	→	→	→	→
Flecainide	?→	?→	?→	→
Lorcainide	↓	↓	↓	↓

of contractility appears to be related to the quinidine concentration. Only minor negative inotropic effects were seen at clinically relevant plasma levels, with significant depression of contractility noted only at considerably higher levels.[1–3]

Most in vivo studies have revealed both direct myocardial and peripheral vascular effects that are important in the overall hemodynamic response to intravenous quinidine. In almost all intact animal models, intravenous quinidine produces significant peripheral vasodilation.[6–15] Schmid et al[14] demonstrated that the peripheral vasodilating effect is produced by 2 independent mechanisms. One is by a direct action to relax vascular smooth muscle and the other is by alpha-adrenergic blockade producing inhibition of adrenergic constrictor tone.[15]

These findings explain the significant decrease in blood pressure and systemic vascular resistance seen after the administration of intravenous quinidine in laboratory animals.[6–15] An animal study of the hemodynamic effects of oral quinidine[16] did not reveal any effect on blood pressure after 10 days to 2 weeks of therapy.

Conclusions from studies evaluating quinidine's effects on myocardial contractility are considerably more variable and the mechanisms more complex. Most animal studies evaluating myocardial contractility with the use of a myocardial strain gauge, by measurement of peak first derivative of left ventricular (LV) pressure (dP/dt) or by measurement of cardiac output, have found that intravenous quinidine depresses myocardial contractility transiently.[7,11,12,17] However, others have shown no significant change[9,10] or an increase[8,13] and some have yielded variable results from subject to subject.[6]

Several important studies help to clarify these apparently contradictory results. Folle and Aviado[6] reported a variable effect on myocardial contractility from animal to animal and had 3 dogs in which an increase in contractility was abolished by adrenalectomy. In 2 other studies,[8] intravenous quinidine alone produced an increase in myocardial contractility compared with control values. However, after propranolol, intravenous quinidine produced either a decrease[8] or no change[13] in contractility. These investigations support the concept that quinidine has no direct positive inotropic effect, but produces reflex sympathetic stimulation secondary to the hypotension it induces. Unfortunately, not all studies have shown these results. A study by Stern[11] showed a combination of propranolol and quinidine to produce less depression of myocardial contractility than either drug given alone. O'Rourke et al[16] found no change in myocardial contractility in dogs treated for 2 weeks with oral quinidine.

Few hemodynamic studies of quinidine have been performed in man. One study of 5 heart transplant recipients[18] evaluated the effects of intravenous quinidine. The study revealed a significant decrease in blood pressure and cardiac output and, using an assumed right atrial pressure, no change in systemic vascular resistance. Intravenous quinidine decreased both end-systolic and end-diastolic volumes without any change in ejection fraction. The investigators interpreted their results as demonstrating a possible effect of quinidine to increase venous capacitance, leading to decreased preload with the expected hemodynamic results. The lack of any effect of quinidine on systemic vascular resistance in that study is not well explained.

Several studies of the effects of oral quinidine have been performed both in normal volunteers[19–21] and in patients with heart disease.[20–22] Overall, oral quinidine in standard antiarrhythmic doses has few clinically important hemodynamic effects as assessed by noninvasive methods. One early study[21] used a single 800-mg

oral dose of quinidine and showed a significant decrease in blood pressure with a concomitant decrease in systemic vascular resistance in many patients. Patients with a poor cardiac output at rest had an improved cardiac output, whereas those with normal cardiac output at rest had a decrease. This may again be due to an effect on capacitance and resistance vessels to produce both a decrease in preload and afterload with its consequent hemodynamic effects.

Overall, oral quinidine in standard doses appears to be well tolerated, without significant adverse hemodynamic effects, even in patients with LV dysfunction. This conclusion is supported by results of the Boston Collaborative Study,[23] in which 652 patients taking quinidine had no exacerbation of congestive heart failure despite a predrug incidence of 35%. The primary hemodynamic effect of intravenous quinidine is peripheral vasodilation of both capacitance and resistance vessels. Its effect on cardiac output will depend on the balance between changes in preload and afterload and the patient's preexisting hemodynamic state. There is usually a significant decrease in systemic blood pressure, which can often be avoided by rapid volume expansion during the quinidine infusion. Although quinidine does exert a mild negative inotropic effect, this may be offset by a reflex increase in sympathetic tone and is of less clinical importance than the drug's peripheral effects.

Procainamide

Studies of the hemodynamic effects of procainamide have also yielded conflicting results. An in vitro study of its effect on an isolated papillary muscle preparation showed no negative inotropic effect at concentrations equivalent to clinically effective plasma levels and an increase in contractility at higher concentrations.[1] This has not been observed in studies on intact animals.

Most in vivo animal studies demonstrate a negative inotropic effect after large doses of intravenous procainamide.[6–8,24,25] Most also show a significant decrease in systemic blood pressure,[6–8,24–26] without a significant decrease in systemic vascular resistance.[8,25] At similar doses, however, some studies have shown no significant hemodynamic effects of intravenous procainamide[27] and others have shown a negative inotropic effect only at high doses, with a positive inotropic effect observed at lower doses.[26] Despite the lack of effect on systemic vascular resistance in these studies, the ability of procainamide to produce vasodilation is well known.[6,28] Why its peripheral effects were not clearly seen in all studies is not known.

The hemodynamic effects of intravenous procainamide in man have been studied extensively.[29–37] The effects seen relate not only to the total dose administered but to the rate of administration.[31] Several studies have shown that the drug has a negative inotropic effect at therapeutic doses.[29,33,34,37] One study[29] of intravenous procainamide in patients undergoing cardiac surgery showed decreases in contractility (measured by the use of a strain gauge sutured to the right ventricle) at doses of 2 and 4 mg/kg. Most other studies have also found that the myocardial depression is dose-related.[29,34] Only occasional studies have demonstrated a decrease in cardiac output,[33,34] and these changes have generally been small and not of clinical significance. Although this degree of decrease in contractility is of minor importance at the doses generally used, the possibility of more serious clinical effects at higher doses does exist.

Most studies in man have shown a significant decrease in systemic blood pressure after the administration of intravenous procainamide,[29,33–36] but others have shown little, if any, effect.[30–32] The difference may again relate to the total dose and the rate of administration. The decrease in blood pressure is thought to be related to peripheral vasodilation, but no consistent change in systemic vascular resistance has been observed.[33,34]

Overall, at usual antiarrhythmic doses, procainamide has a mild-to-moderate negative inotropic effect and produces a transient decrease in systemic blood pressure. The effects appear related to both total dose and rate of administration. In general, it is well tolerated even in patients with LV dysfunction or acute myocardial infarction.[25,31,32] However, the possibility of clinically important effects at high doses in patients with severe LV dysfunction exists, and procainamide should be used with caution under these circumstances.

Lidocaine

One in vitro study assessing the effect of lidocaine on the isometric contractile force of isolated cardiac muscle had demonstrated a negative inotropic effect[1] and another found little or no depressant effect.[3] The concentration of lidocaine used varied between these 2 studies, and decreased contractility was seen only with concentrations greater than those used clinically.[1]

Hemodynamic evaluations in intact animals have shown similar results. Assessment of LV function after administration of intravenous lidocaine by the measurement of changes in peak dP/dt,[12,24,25,38] by the use of a myocardial strain gauge,[12,26] or by the construction of ventricular function curves[24] have all demonstrated similar effects. Lidocaine in doses frequently used in clinical practice has little, if any, hemodynamic effect. The changes observed have consisted of very small transient and clinically insignificant decreases in LV contractile force,[26] LV peak dP/dt[38] and systemic blood pressure.[26,39] These minor changes all returned to control values by 5 to 10 minutes after a bolus was administered.

These investigations all show that at very high doses (4 to 40 mg/kg), lidocaine demonstrates dose-related myocardial depression.[12,24–26,38] Statistically and clinically important decreases in contractile force,[12,26] LV peak dP/dt,[12,24,25,38] cardiac output[25] and systemic blood pressure[12,24–26,39] were consistently seen at doses that would be toxic in man.

Many clinical studies have evaluated the hemodynamic effects of lidocaine.[29,31,32,40–44] The population used for each investigation was different, but in several studies lidocaine was administered to patients undergoing hemodynamic monitoring during an acute myocardial infarction[31,32,40,43] or to patients with coronary

artery disease or significant LV dysfunction.[31,41,42] Even in this group of patients, in which one would expect to see the most dramatic results of any adverse hemodynamic effects, no clinically significant changes in myocardial function or systemic blood pressure were observed.

These data support the long-standing clinical experience that standard doses of intravenous lidocaine can be used safely without untoward hemodynamic effects, even in patients with acute myocardial infarction and severe LV dysfunction. Although sensitive measurements can detect a mild myocardial depressant effect, this rarely is of clinical significance at the doses generally used. The experimental studies do demonstrate that at very high levels, lidocaine can exert significant negative inotropic effects.

Bretylium

Bretylium is unique among the antiarrhythmic agents in that short-term studies on isolated cardiac muscle,[1,45–48] in intact animals[49,50] and in man[51] have all shown that it possesses a positive inotropic effect on cardiac muscle.

In vitro studies on isolated papillary muscle preparations have shown that bretylium concentrations similar to those used in clinical medicine have a dose-related positive effect on contractile force.[1,45–48] Pretreatment of animals with reserpine to produce catecholamine depletion or the addition of propranolol to the bath prevent this positive inotropic effect,[45,46] suggesting that bretylium's positive inotropic effect is not a direct effect but rather the result of myocardial catecholamine release. Other studies have shown both a direct and an indirect effect leading to increased contractility.[48] There is little question, however, that myocardial catecholamine release plays a major role. It may be that at lower doses, this effect is primary and that at higher doses a direct positive inotropic effect occurs.[52]

Several in vivo animal investigations support the conclusions from the in vitro studies.[49,50] A canine study by Gilmore and Siegel[50] demonstrated an immediate decrease in LV end-diastolic pressure after the administration of bretylium at a time when heart rate and cardiac output were constant, a finding interpreted as consistent with an increase in contractility. During this period, coronary venous blood samples showed a consistent increase in catecholamine content, followed by an increase in arterial catecholamine concentration. After the injection of bretylium, stimulation of cardiac sympathetic efferent nerves produced little cardiac response and little or no increase in myocardial catecholamine release compared with pre-bretylium values. This effect was not simply due to catecholamine depletion, because tyramine caused an adequate catecholamine release. The mechanism of this blocking action is unknown.

The early positive inotropic effect of bretylium was demonstrated in man by Jorgensen et al,[51] who showed that an intravenous infusion produced an immediate increase in cardiac index, arotic pressure and LV peak dP/dt. However, 30 minutes after the infusion, the aortic pressure and cardiac index had returned almost to control values and the peak dP/dt was past its maximum and beginning to decrease. The prior administration of propranolol blocked most of these effects, again suggesting the role of catecholamine release.

In a subsequent investigation by Chatterjee et al,[45] bretylium was given to patients within 72 hours of an acute myocardial infarction and hemodynamic variables were studied for 2 hours. There was an early increase in blood pressure and heart rate accompanied by an increase in systemic vascular resistance. However, no change in cardiac index or intracardiac pressures was observed. Two hours after the infusion, blood pressure, systemic vascular resistance and heart rate were all below control values, still with no significant change in cardiac index or filling pressures.

Bretylium's most clinically important hemodynamic effect in man is orthostatic hypotension, which can often be profound. A study by Taylor et al,[53] in which 62 patients with acute myocardial infarction were treated with bretylium, demonstrated hypotension to be a common finding. In one third of their patients, the drug had to be discontinued as a result of this adverse effect. Other investigators did not find this to be a problem, especially when their patients remained supine.[54,55] The hypotension probably results from adrenergic neuronal blockade, but its mechanism is not fully understood.

In summary, the positive inotropic effect of bretylium, although unique, is transient and probably of little clinical importance in most situations. The subsequent persistent decrease in blood pressure, especially in the upright position, is much more clinically relevant. It is well tolerated by many patients, but can lead to severe consequences, especially in those patients with low or fixed cardiac output on the basis of valvular heart disease or severe LV dysfunction. It must be used with care in these situations.

Disopyramide

Disopyramide has a negative inotropic effect, both in in vitro experiments using isolated cardiac muscle[56] and in studies in intact animals.[9] In one recent study in unanesthetized dogs,[9] intravenous disopyramide produced dose-related decreases in LV peak dP/dt and stroke volume and significant increases in heart rate, systemic vascular resistance and blood pressure. These changes occurred within 1 minute of injection and persisted for about 30 minutes. No significant change in cardiac output was observed. The investigators believed the changes were to a degree that could produce clinically important adverse effects in man.

These concerns have been shown to be well founded in many studies of disopyramide in man[44,57–69] and are expressed in several recent reviews.[70,71] Almost all studies show that disopyramide exerts a negative inotropic effect[44,57–63,69,72] in association with a direct effect to increase systemic vascular resistance.[44,58–61,63,73] The only differences from study to study have been differences in the severity of these changes, and this variation probably reflects differences in the patients being evaluated. The hemodynamic changes observed included increases in systemic blood pressure, decreases

in cardiac index and stroke volume, and increases in intracardiac filling pressures.

Disopyramide causes small but significant increases in LV filling pressures and decreases in cardiac index in normal subjects[62] and in patients with poor LV function, the changes are even more remarkable.[58–60,63] Occasional dramatic decreases in cardiac output associated with severe hypotension have been noted.[60]

Studies of oral disopyramide indicate that the cardiac depressant effects of this drug are not unique to the intravenous preparation.[65–69] Reports of cardiogenic shock[67,68] and electromechanical dissociation[66] due to disopyramide demonstrate the potential for disastrous results associated with the use of this drug in patients with severe abnormalities of LV function.

Podrid et al[65] describe the clinical follow-up study of 100 patients who began taking disopyramide for the control of arrhythmias; they emphasize the importance of careful patient selection before the use of this drug. In their group of patients, 62 were taking disopyramide for only several days and the remainder were treated on a long-term basis with 9 months of follow-up evaluations. In 16 of the original 100 patients, clinical congestive heart failure developed during this period, in 3 during the first 48 hours and in 13 during long-term treatment, usually within 3 weeks of beginning the drug. In 55% of the patients with a history of congestive heart failure, congestive heart failure again developed with disopyramide therapy. Only 2 patients without such a history had congestive heart failure while taking this drug.

Disopyramide combines a significant negative inotropic effect with a peripheral vasoconstrictive effect that results in some adverse hemodynamic effects in most patients. The changes are of little clinical consequence in patients with well-preserved LV function; however, patients with LV dysfunction and a history of congestive heart failure have a high propensity for clinical deterioration, and disopyramide should be avoided in these patients.

Phenytoin

Two studies of the effects of phenytoin (formerly diphenylhydantoin) on the isometric force of contraction of isolated cardiac muscle[1,74] have shown a significant negative inotropic effect. In one of these,[1] phenytoin had the most significant depressant effect on contractility of any of the drugs evaluated, including propranolol.

Studies in animals have generally shown 2 primary effects: a mild, transient, negative inotropic effect and a transient decrease in blood pressure.[17,74,75] The decrease in contractility appeared to be dose-related[17,74,75] and lasted for 3[75] to 60 minutes.[74] This effect was probably clinically important only at large doses. A transient decrease in systemic arterial pressure was observed in most studies using intravenous phenytoin[75,76] and appears to be due primarily to peripheral vasodilation.[74] This effect is unchanged by denervation[75] or beta blockade[74] and is considered due to a direct action of phenytoin on the peripheral vasculature. Sanbar et al[76] demonstrated that the degree of hypotension after the administration of phenytoin was not only related to total dose, but more importantly, to the rate of administration of the drug. This may account for many of the differences seen between studies in both animals and man.

Findings of hemodynamic studies of phenytoin in man agree with those of animal investigations. In general, the use of intravenous phenytoin has been associated with a transient, mild, negative inotropic effect[30,77] and, occasionally, a brief decrease in systemic blood pressure.[30,78] However, some studies found no evidence of decreased contractility[79] or change in blood pressure.[77,79] These differences may be related to the population studied or the rate of administration of the drug, as demonstrated by Mierzwiak et al.[80]

Most of these studies have been done in patients with well-preserved LV function and relatively small doses of phenytoin were used. When hemodynamic effects occurred, they were so mild and so transient as to be clinically inconsequential. High doses of this agent in patients with severely compromised LV function could result in more apparent detrimental clinical effects.

A report by Mercer and Osborne[78] of 6 years of clinical experience with phenytoin for the treatment of arrhythmias supports the conclusions of the hemodynamic studies. Over this period, intravenous phenytoin was used to treat 774 episodes of arrhythmia. They describe only a rare occurrence of mild, transient hypotension and no precipitation or exacerbation of congestive heart failure. The drug was administered during monitoring of intracardiac pressures in >130 of these episodes and there were no significant effects observed on pulmonary artery pressure.

In summary, phenytoin in the doses most often used is safe and well tolerated by most patients. It exhibits a mild negative inotropic effect that is generally of little clinical significance even in patients with moderate degrees of LV dysfunction. The hypotension produced by the intravenous infusion of this drug appears to be related not only to total dose, but more importantly, to the rate of administration. It can be almost completely avoided by using slow infusion rates (<25 mg/min) and by avoiding rapid bolus injections. Phenytoin has produced few untoward hemodynamic responses during its long period of clinical use.

Calcium Antagonists

There are a number of recent reviews of the use of the calcium antagonists.[70,71,81–84] These drugs demonstrate a great interplay of direct and indirect hemodynamic effects. The overall outcome in any subject is difficult to predict and depends on the relative contribution of these direct effects and reflex responses. This fact makes comparison of one study to the next and the interpretation of their results difficult. Nevertheless, certain responses are consistently observed during the use of these drugs.

In vitro studies of perfused hearts and isolated cardiac muscle have shown negative inotropic and chronotropic effects of all the calcium antagonists in general use (nifedipine, verapamil and diltiazem);[85] only the degree of these effects varied from agent to agent.

In animals, calcium antagonists cause a dose-related decrease in systemic vascular resistance and blood pressure[86–91] owing to a direct peripheral vasodilating action. The effects on contractility are not quite as consistent. In vivo studies with diltiazem have generally shown no significant change in LV peak dP/dt;[85,86] nifedipine has produced an improvement[89] and verapamil has generally caused some decrease.[85,90,91]

The chronotropic effects of diltiazem and verapamil in animals have varied from study to study. Most investigators have shown a dose-related decrease in heart rate,[88,90,91] some have demonstrated no change,[86,89] and one showed an increase in heart rate for both of these agents as well as for nifedipine.[85] An interesting study by Bourassa et al[86] highlights the interplay of the direct and reflex effects of these drugs. Intravenous diltiazem administered to anesthetized dogs produced no change in heart rate despite a 30% decrease in mean aortic pressure. When aortic pressure was returned to control levels by mechanical constriction, the resulting heart rate decreased to 85% of the control value. Their conclusion was that the direct negative chronotropic effect of diltiazem was masked by the reflex increase in heart rate resulting from the drug-induced decrease in systemic arterial blood pressure.

Almost all studies in man show a substantial decrease in blood pressure and systemic vascular resistance immediately after intravenous administration[86,92–102] and demonstrate that this effect is not abolished by beta-adrenergic blockade.[101,102] Similar results have been observed with a different time course after oral administration.[103–105] Most investigators have found a decrease in LV peak dP/dt after the administration of a calcium antagonist[93,97,98,101] and many have reported an increase in LV end-diastolic pressure.[93,96–98] In spite of these findings, cardiac index increased in most studies in which it was evaluated[92,94–96,98,103] and was found to decrease or remain unchanged primarily when beta-blocking drugs were given in conjunction with the calcium antagonists.[101,102,105]

The extent of these hemodynamic changes at the standard doses used have generally been small and well tolerated. However, the potential for clinical deterioration in some patients with severe LV dysfunction who are treated with calcium antagonists does exist.[99]

The effects of the calcium antagonists on heart rate in man have been studied in several investigations, with variable results.[86,92–99,101–105] In most, diltiazem and verapamil produced no consistent change in heart rate.[92,94,96,97,99,104] Others have shown a slight increase in heart rate[93,95,98,103] and some have shown a decrease,[86] especially in conjunction with beta-blocking drugs.[101,105] Most of these changes have been small and of little clinical significance.

In general, in man verapamil appears to have a greater overall negative chronotropic effect than diltiazem, and nifedipine usually produces a small increase in heart rate due to its potent peripheral vasodilating effect. In any given patient, however, the effect on heart rate for any of these agents is difficult to predict.

In summary, the hemodynamic effects of the calcium antagonists result from a complicated interaction of direct and reflex effects. All of the agents produce peripheral vasodilation by direct action on the vasculature. This produces a reflex increase in sympathetic tone, leading to an increase in myocardial contractility and heart rate. These positive inotropic and chronotropic effects may be offset by direct negative inotropic and chronotropic effects. The net result depends on the particular agent used, the particular patient involved and the interplay of the various factors. In most patients, the calcium antagonists do not exert serious adverse hemodynamic effects. However, some patients with severe LV dysfunction may have clinical deterioration. In this group of patients calcium antagonists must be used with caution.

Amiodarone

Several reviews[70,71,106,107] and a number of clinical studies[108–114] suggest that the hemodynamic effects of amiodarone are related to its total dose as well as to the baseline cardiovascular state of the patient in whom it is used. The use of intravenous amiodarone has been assessed in patients with various degrees of LV dysfunction. In most of these, a dose of 5 mg/kg of amiodarone was given as a bolus,[108,109,113,114] and in some this was followed by a constant infusion.[109,113] A decrease in arterial pressure was noted in most patients,[108,113,114] but an occasional investigation revealed no significant change in this measurement.[109] The rate of drug administration correlated with the decrease in systemic blood pressure in some patients.[108] Although most data have shown that the decrease in arterial pressure is due to peripheral vasodilation with an associated decrease in systemic vascular resistance,[70,71,106–108] some studies have demonstrated little or no change.[109,114] Most studies have also revealed a moderate decrease in heart rate associated with intravenous administration of amiodarone.[109,114]

Few studies have made careful measurements of changes in myocardial contractility after administration of intravenous amiodarone. A study in intact dogs demonstrated that a dose of 10 mg/kg had a negative inotropic effect as measured by a decrease in LV peak dP/dt.[115] Studies in patients using smaller doses of amiodarone have shown variable results. Some have shown increases in cardiac index and decreases in LV end-diastolic pressure,[108] and others have shown slight decreases in cardiac index and small increases in pulmonary capillary wedge pressure.[109,114] The differences may well be a result of differences in the baseline LV function of those patients being evaluated. In these intravenous studies, no exacerbation or precipitation of clinical congestive heart failure was seen, even in patients with severe LV dysfunction.[108,109,113] However, an occasional patient did have severe hypotension that required temporary pressor support.[114]

Investigations of oral amiodarone have demonstrated similar results.[110–112] Doses of amiodarone of 200 to 1,200 mg/day did not produce the deterioration or appearance of congestive heart failure, even in patients with severe LV dysfunction followed for as long as 22 months.[111] No detailed hemodynamic data are supplied in these studies, but in general, the drug appeared well

tolerated. In one study 3 deaths from progressive congestive heart failure were reported during 13 months of follow-up, but the association with amiodarone therapy in those patients was not described.[112] Some investigators have also found a modest negative chronotropic effect of oral amiodarone.[110]

Overall, both oral and intravenous amiodarone is well tolerated in most patients. It does exhibit mild negative inotropic and chronotropic effects and its intravenous administration produces peripheral vasodilation with a decrease in arterial blood pressure. In most situations, these effects are not of clinical importance. However, with high doses or rapid infusion rates and in patients with severe LV dysfunction, the potential for significant hypotension does exist.

Mexiletine and Tocainide

Investigations on the hemodynamic effects of mexiletine[116–122] and tocainide[123–128] have generally shown similar results. The use of intravenous mexiletine in animals[118] and in man[116,117,120–122] has produced few significant hemodynamic effects. Small decreases in arterial pressure and LV peak dP/dt and small increases in LV end-diastolic pressure have been observed in some studies,[118,120] but in almost all cases these have been so mild and transient as to be of no clinical significance. Cardiac output has generally remained unchanged. One study by Saunamäki[117] did include 2 patients who had a significant decrease in arterial blood pressure associated with a decrease in systemic vascular resistance and 2 other patients who had significant increases in pulmonary capillary wedge pressure. Even in these patients, no clinical deterioration was seen. The significant changes in these hemodynamic measurements after intravenous mexiletine administration in this investigation are unusual and may be related to the severe degree of LV dysfunction of those 4 patients before drug administration.

Kuhn et al[119] examined the hemodynamic effects of a single large dose of mexiletine administered orally to a group of patients with coronary artery disease. They found no clinically or statistically significant changes in systemic or pulmonary artery pressure or in cardiac output for up to 6 hours after the dose was given.

Tocainide also causes mild and usually clinically unimportant hemodynamic effects. The use of the drug intravenously produces small decreases in LV peak dP/dt[125,127] or small increases in LV end-diastolic[123] or pulmonary capillary wedge pressure.[127] Some investigators have also reported slight increases in systemic vascular resistance.[123,126] Measurements of cardiac output have generally shown no change before and after administration of the drug.[123,125,127]

Large doses of tocainide administered orally to anesthetized dogs produced decreases in LV peak dP/dt and aortic flow and increases in LV end-diastolic pressure.[124] Even these large doses produced only small to moderate effects and small doses produced no measurable hemodynamic changes. Oral tocainide in man has produced no significant hemodynamic effects even in patients with acute myocardial infarction,[126] and has not caused any change in echocardiographic dimensions when administered to patients with valvular heart disease.[128]

Overall, mexiletine and tocainide in both oral and intravenous form have been well-tolerated hemodynamically, even in patients with moderately severe LV dysfunction. They both have mild negative inotropic effects, but these have not been shown to be of clinical importance.

Encainide, Flecainide, Lorcainide

Hemodynamic evaluations of encainide, flecainide and lorcainide have been few, but their results are similar. Intravenous encainide given to patients with varying degrees of LV dysfunction produced little or no negative inotropic effect and had little or no effect on systemic vascular resistance.[129] Oral encainide similarly produced no significant change in radionuclide ejection fraction at rest or during treadmill exercise in a group of patients with fairly well preserved LV function.[130]

Flecainide has been less systematically evaluated. When administered intravenously to anesthetized pigs, decreases in LV peak dP/dt and cardiac output were observed and appeared to be dose-related.[131] In man, only oral flecainide has been studied and only its effects on echocardiographic parameters have been evaluated.[132–134] No detailed hemodynamic studies have been done. Nevertheless, these investigations showed oral flecainide to be well tolerated, without significant effects on blood pressure or echocardiographic measurements in patients with fairly well preserved LV function.[132–134] No clinical deterioration or change in exercise tolerance was observed.[134]

Intravenous lorcainide has been evaluated in more detail. It produces decreased contractility of isolated papillary muscles studied in vitro.[135] In vivo studies in dogs have shown that it causes transient decreases in LV peak dP/dt, systemic arterial blood pressure and systemic vascular resistance and, at high doses, occasionally produces significant increases in LV end-diastolic pressure.[135]

Studies of intravenous lorcainide administered to man have demonstrated small decreases in LV peak dP/dt[136] and cardiac output.[136,137] In the study by Meinertz et al,[136] angiographically determined LV ejection fraction decreased by a small amount in almost all patients after intravenous lorcainide was administered. In all of these investigations, the changes were small and of little clinical significance in the groups of patients studied.

In summary, encainide, flecainide and lorcainide appear to be well tolerated hemodynamically when administered to patients with fairly well preserved LV function. However, all exert a mild negative inotropic effect and must be used with care in patients with severely compromised LV contractility or poorly compensated congestive heart failure. The dearth of systematic hemodynamic studies in these groups of patients makes it impossible to realistically assess the risk of using these agents in such patients. Certainly, the theoretical risk of clinical deterioration exists and appropriate caution must be exercised.

Conclusion

Antiarrhythmic drugs are often used in patients with organic heart disease who have varying degrees of LV dysfunction and who have overt or compensated congestive heart failure. Most antiarrhythmic agents, with the exception of bretylium, have mild or moderate negative inotropic effects when examined by sensitive methods. In practice, however, most of these drugs, with the possible exception of disopyramide, when used at standard doses rarely produce clinically important hemodynamic effects. However, in patients with severe LV dysfunction or when high doses are required, the hemodynamic effects may become clinically important. In these circumstances, the basic characteristics of each agent must be examined to choose the most appropriate drug.

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Clinical Profiles of Newer Class I Antiarrhythmic Agents—Tocainide, Mexiletine, Encainide, Flecainide and Lorcainide

ANTHONY POTTAGE, MRCP

New class I antiarrhythmic drugs differ in potency, adverse effects and pharmacokinetics. Encainide and flecainide can totally suppress arrhythmias in some patients, but arrhythmia induction can also occur. At effective dose levels, neurologic and gastrointestinal adverse effects are uncommon. Flecainide pharmacokinetics are suitable for oral use but encainide disposition is complex with variable bioavailability and active metabolites that contribute substantially to activity. Lorcainide is also potent, but neurologic adverse effects are common and dose-dependent bioavailability and an active metabolite may complicate long-term oral therapy. Tocainide and mexiletine can suppress arrhythmias in acute myocardial infarction, during convalescence from myocardial infarction and in patients with arrhythmias resistant to other therapy. Dose-related neurologic and gastrointestinal adverse effects are common, but hemodynamic effects are minor and arrhythmia induction is rare. Tocainide disposition is reasonably predictable and stable in patients, but mexiletine disposition is less so because of variation in distribution and clearance. Although all of the newer agents have some disadvantages, their availability should increase the likelihood of success in the high-risk patient.

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All antiarrhythmic agents available for general use in the United States—lidocaine, quinidine, procainamide, disopyramide and beta-adrenergic antagonists—have properties that limit their clinical value. Although no drug totally suppresses arrhythmias in all patients, all are accepted as having useful antiarrhythmic activity. Other factors, such as pharmacokinetic properties inappropriate for oral use, impairment of intracardiac conduction, negative inotropic effects, and dose-related or idiosyncratic adverse effects, are the major limitations to their use.

Identification of these problems has resulted in a search for new antiarrhythmic drugs that offer equal or greater potency with fewer clinical limitations, and a number of agents are undergoing active development. The agents described in this review—tocainide, mexiletine, encainide, flecainide, and lorcainide—are class I drugs that reduce the rate of increase of Purkinje and ventricular action potentials by inhibiting the fast sodium channel.[1]

Tocainide

Tocainide is an analog of lidocaine that has similar antiarrhythmic, hemodynamic and electrophysiologic effects, but with pharmacokinetic properties suitable for oral use.

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Electrophysiologic and hemodynamic effects: Tocainide shortens action potential duration[2] and the effective refractory periods of the atria, atrioventricular node and ventricles.[3] It has little effect on sinus nodal automaticity or intracardiac conduction,[4] even in patients pretreated with a beta-adrenergic antagonist.[5] Although PR and QRS intervals are usually unchanged, tocainide may reduce the QT interval.[6] Cardiac hemodynamic effects are minor, even in patients with moderate left ventricular dysfunction[7] and those also receiving a beta antagonist.[5] In the acute stages of myocardial infarction (MI), the hemodynamic effects of tocainide are quantitatively similar to those of lidocaine and are determined by the rate of administration and by plasma concentration.[8]

Antiarrhythmic effects: Table I is a list of the effects of tocainide on the frequency of ventricular premature complexes (VPCs) as reported in a number of studies. The percentage of patients who showed >70% VPC suppression varied from 11 to 75% (mean 58), and in those who responded the VPC frequency decreased by 86 to 94%. In 1 study, concentrations <3.5 μg/ml produced <50% VPC suppression, and concentrations of about 8.5 μg/ml approximately 90% suppression. There was little further increase in activity with higher concentrations.[9] A similar relation between concentration and response was reported by Roden et al.[19]

TABLE I Oral Tocainide—Effects on Frequency of Ventricular Premature Complexes in Patients with Chronic Ventricular Arrhythmias

Reference	Dose (mg)	No. of Patients		Mean % VPC Suppression	
		Total	>70% VPC Suppression	Responders*	Overall
Winkle et al[9]	400 q8h	15	8 (53%)	...	...
	600 q8h	15	11 (73%)	...	...
Woosley et al[10]	400–1,100 q12h	12	8 (67%)	86	...
Fagan et al[11]	400–600 q8h	15	7 (47%)	...	...
Ryan et al[12]	400–800 q8h	27	13 (48%)	94	60
Engler et al[13]	400–800 q8h	20	15 (75%)	94	84
Sonnhag[14]	400 q8h	18	11 (61%)	...	...
Wasenmiller and Aronow[15]	600 q8h	9	1 (11%)	...	...
LeWinter et al[16]	400–800 q8h	10	7 (70%)	93	65
Hanrath and Kuck[17]	400–600 q8h	12	...	...	66
Sigurd et al[18]	400 q8h	12	...	...	51
	600 q8h	12	...	...	69

* >70% ventricular premature complex suppression.
VPC = ventricular premature complexes.

In 17 patients treated with tocainide for up to 27 months, symptoms were abolished in 7 of 9 with sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or both and in 1 of 3 with symptomatic nonsustained VT.[20] In a similar group, tocainide abolished the arrhythmia in 14 of 21 patients with recurrent VT, and in 8 of the 11 in which the arrhythmia was symptomatic.[13] Tocainide can be effective in patients with arrhythmias unresponsive to other oral therapy,[19,21,22] and a response to lidocaine may predict responsiveness to tocainide.[19]

Since 1974, oral tocainide has been available in the United States for emergency use in patients unresponsive to or intolerant of quinidine, procainamide, propranolol and, recently, disopyramide. To qualify for treatment, patients had to have sustained VT, paroxysmal VT or VF, R-on-T VPCs, multifocal VPCs (>6/min) or symptomatic unifocal VPCs (>15/min). Data on the initial response to tocainide are available for 1,236 patients (Assaykeen T, Pottage A, Irvin JD, Schrogie JJ: unpublished observations). Fifty-six percent had >75% suppression of VPCs, 27% had <75% suppression and 17% had no response or an increase in arrhythmia frequency. Of 1,206 patients discharged from the hospital taking tocainide, 509 gave a history of emergency hospital admission for VT/VF, 390 a history of emergency cardioversion and 407 a history of syncope before enrollment in the program. Eighty-seven patients were readmitted to the hospital for VT/VF while receiving treatment with tocainide, 60 required cardioversion and 89 reported syncopal attacks.

In acute MI, tocainide suppresses "warning" arrhythmias with activity similar to that of lidocaine.[23] Prophylactic tocainide can suppress VT and frequent (>30/hour) VPCs in the first 24 hours of coronary care unit admission for MI[24,25] (Fig. 1). When given over a 6-month period after MI, oral tocainide prevents the increase in VPC frequency that occurs during mobilization.[26]

Pharmacokinetics and dosage regimens: Tocainide differs from lidocaine in that it has pharmacokinetic properties suitable for oral use (Table II). Its bioavailability is high, indicating little presystemic elimination, and absorption is rapid even in patients with acute MI.[27] Absorption is not dose-dependent and although the rate is reduced by food, the extent of absorption is unchanged.[28] Tocainide is rapidly distributed, with a total apparent volume of distribution of 2 to 4 liters/kg. There is little binding to plasma proteins (10 to 20%) and tocainide, unlike lidocaine, does not bind to alpha 1-acid glycoprotein.[29] Elimination is not dose-dependent and occurs by both renal excretion of unchanged drug (approximately 40%) and hepatic metabolism. The mean systemic clearance is about 120 ml/min in patients with chronic ventricular arrhythmias (Fig. 2) and the mean half-life is approximately 15 hours.[9–11,18,27] Tocainide clearance decreases predictably in patients with renal dysfunction, the mean half-life increasing to approximately 30 hours and the

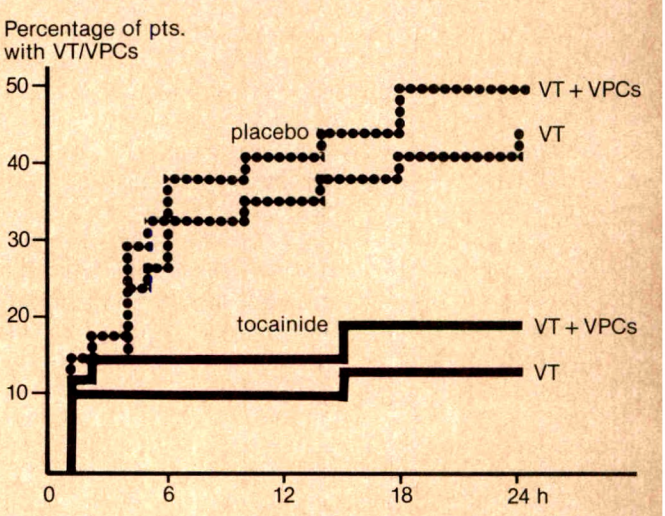

FIGURE 1. Cumulative incidence of ventricular tachycardia (VT) and frequent ventricular premature complexes (VPCs; >30 beats/min) over the first 24 hours of hospital admission in 31 patients with acute myocardial infarction given tocainide (750 mg intravenously, 800 mg orally then 400 mg every 8 hours) and in 34 given placebo. Reproduced from Rydén et al.[25] with permission of the publisher.

TABLE II Pharmacokinetic Properties of New Class I Antiarrhythmic Drugs

Drug	Bioavailability	Approximate Half-Life (hours)	Approximate Distribution Volume (liters)	Total Clearance (ml/min/kg)	Major Route of Elimination	Active Metabolites
Tocainide	95%	15	200	2.4	Metabolic/renal	No
Mexiletine	85%	11	500	6.5	Metabolic	No
Encainide	42%*	3	200‡	13.2	Metabolic*	Yes
Flecainide	95%	20	. . .	. . .	Metabolic	. . .
Lorcainide	. . .†	8	900	>15.0	Metabolic	Yes

* Probably dose-dependent.
† Dose-dependent.
‡ Value derived from half-life and clearance.

mean total clearance decreasing by about 50% (Fig. 2). The effects of partial renal dysfunction (creatinine clearance 10 to 55 ml/min) are intermediate.[30] Although tocainide metabolites (N-carboxytocainide glucuronide and lactoxylidide) may accumulate in renal failure, they have no significant pharmacologic activity.[31] In chronic liver disease, tocainide elimination is usually only slightly impaired, although significant prolongation of the half-life can occur with acute hepatic necrosis.[32] There appear to be no important pharmacokinetic interactions between tocainide and metoprolol (Granath, A: unpublished observations), digoxin,[12] phenobarbitone, clofibrate, or salicylamide.[33]

The suggested optimal range for tocainide plasma concentrations is 3.5 to 8.5 μg/ml tocainide base (4 to 10 μg/ml tocainide hydrochloride). In most patients, concentrations within this range can be achieved with a dosage of 1,200 to 1,800 mg/day given orally in divided doses every 8 or 12 hours. Tocainide plasma concentrations are relatively stable over long periods in patients with chronic ventricular arrhythmias.[20] However, if dose requirements alter as a result of changes in renal function, plasma concentration monitoring may be helpful to adjust dosage as the relation between dose and steady-state concentration is linear, and tocainide metabolites are not active. Doses of as much as 3,200 mg/day have been used in some patients with resistant arrhythmias, although the incidence of adverse effects is high.[21] Combined intravenous and oral loading doses have been described for emergency use.[23,25]

Adverse effects: The most common dose-related adverse effects in 943 patients given oral tocainide were dizziness (12.5%), paresthesia (6.5%), tremor (5.9%), nausea (14.3%), vomiting (5%) and sweating (5%); in 1 study, adverse effects of this type were noted in about 25% of patients with plasma tocainide concentrations >11 μg/ml.[19] Dose-related adverse effects tend to occur early in the course of treatment and to decrease in frequency and severity over time. They can be minimized by drug administration with food or by taking smaller doses more frequently.[21] Rashes have been reported in 1 to 3% of patients, but other hypersensitivity reactions, convulsions and arrhythmia induction are rare.[34–36]

Mexiletine

Mexiletine is a potent local anesthetic with electrophysiologic and hemodynamic properties similar to those of lidocaine and tocainide.[37,38]

Oral mexiletine and procainamide have similar potency in patients with chronic ventricular arrhythmias.[39] Breithardt et al[40] reported that oral disopyramide was more effective when both mexiletine and procainamide were given at a dose of 600 mg/day, but the difference disappeared when the mexiletine dose was increased. Other studies have confirmed the efficacy of mexiletine in patients with symptomatic arrhythmias not controlled with other therapy.[41–43] In acute MI, intravenous mexiletine may be more effective than lidocaine in suppressing VPCs and VT;[44] prophylactic oral mexiletine suppresses VPCs and VT in both coronary care unit populations[45] and patients treated at home.[46] However, Chamberlain et al[47] reported that of 181 patients recovering from MI, although oral mexiletine significantly reduced the frequency of VPCs 1 and

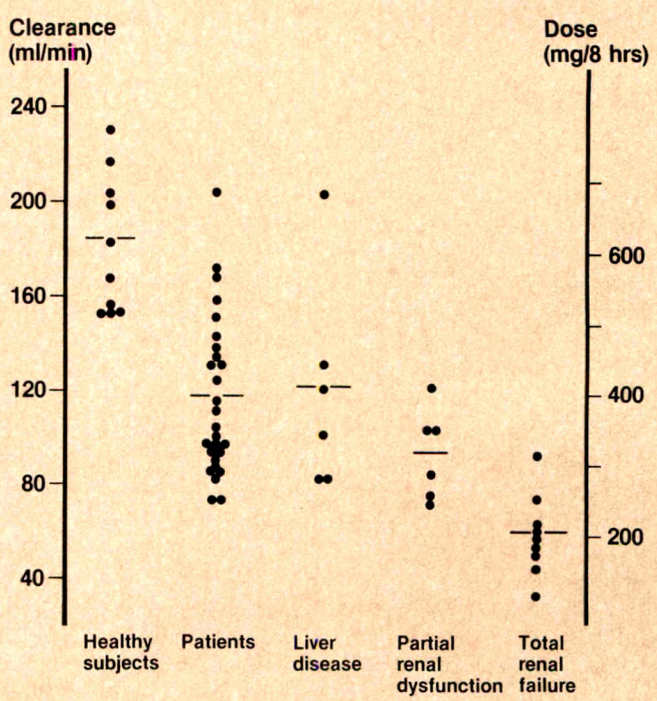

FIGURE 2. Total systemic tocainide clearance (mean shown by vertical bars) and doses (milligrams of tocainide hydrochloride every 8 hours) required to produce a mean steady-state plasma concentration of 6 μg/ml in healthy subjects and patients with chronic ventricular arrhythmias, liver disease and renal dysfunction. Data taken from references 9, 20, 27, 28, 30 and 32.

3 months after inclusion, and the incidence of couplets at 1 month, there was no significant effect on the incidence of VT or R on T VPCs.

Mexiletine differs from both lidocaine and tocainide in its pharmacokinetic properties (Table II). In contrast to lidocaine, it is well absorbed after oral administration and has a long half-life.[48] In contrast to tocainide, it is widely distributed and eliminated mainly by hepatic metabolism. The long half-life of mexiletine results mainly from extensive distribution, that of tocainide from low systemic clearance. Mexiletine absorption is delayed in patients with MI and by narcotics;[48] microsomal enzyme-inducing agents accelerate elimination.[49] Plasma mexiletine kinetics show little change in patients with renal failure,[50] but elimination is significantly impaired in liver disease.[51]

Plasma mexiletine concentrations of 1 to 2 μg/ml are considered optimal[52] and can normally be achieved with oral doses of 200 to 300 mg every 6 to 8 hours. There is considerable interindividual variation in steady-state plasma concentrations, which can vary 5- to 8-fold with a given dose.[52] This is presumably due to the intrinsic variation associated with high clearance and extensive distribution. Large loading doses are necessary to achieve effective levels quickly because of extensive distribution, and the doses required may be poorly tolerated.

Common dose-related adverse effects are neurologic or gastrointestinal and tend to occur early during therapy. In 1 study of 156 patients, minor adverse effects were noted in association with 30% of plasma mexiletine concentrations >2 μg/ml and severe adverse effects (bradycardia, hypotension, atrioventricular dissociation, vomiting and confusion) with 19% of such concentrations.[52]

Encainide

Encainide is a potent antiarrhythmic, structurally unrelated to other agents, that can be given both orally and intravenously. In vitro, encainide markedly reduces the action potential rate of increase, with no effect on the effective refractory period and minimal shortening of action potential duration.[53] In man, encainide prolongs His-Purkinje conduction and PR, HV and QRS intervals, usually with little change in sinus nodal recovery time, AH intervals or effective refractory periods.[54–58] A 10% increase in QT interval was noted in 1 study with intravenous encainide,[54] but not in others and not during short-term oral therapy.[55] Prolongation of the effective refractory period and QT interval during long-term therapy may be due to accumulation of an active metabolite.[56] Encainide produces little depression of cardiac hemodynamics in the absence of cardiac failure.[57,58]

Encainide is very potent and total abolition of arrhythmias has been recorded in 44 to 90% of patients given the drug on a short-term basis.[57,59] Ten responding patients from 1 short-term study continued receiving therapy, with satisfactory arrhythmia control in all patients for 6 to 12 months (mean 8).[57] However, in another study, long-term encainide therapy was evaluated in 38 patients with recurrent, symptomat VT; in 11, arrhythmias recurred within 1 month starting therapy.[60] Suppression of supraventricul extrasystoles and paroxysmal atrial tachycardia has al been reported.[54]

Encainide absorption is variable, probably becau of saturable presystemic elimination.[61] The total sy temic clearance is high but also variable, and the hal life is short (Table II). In 1 study, steady-state plasm concentrations were not linearly related to dos suggesting dose-dependent elimination.[57] Encainide extensively metabolized and 2 highly active metabolit accumulate to higher levels than the parent drug duri long-term therapy.[62] The effective dose has been r ported as 75 to 300 mg/day, given in divided doses eve 4 to 6 hours,[57,60,61] although frequent dosing may be le important during long-term therapy because of m tabolite accumulation. Antiarrhythmic plasma co centrations of encainide vary as much as 50-fold[61] an optimal concentrations for the metabolites are u known. Dosage should be adjusted on the basis of r sponse (arrhythmia suppression, QRS widening) an tolerance.[60]

Encainide is usually very well tolerated, and the rat of effective to toxic plasma concentrations is high.[60,] Dose-related adverse effects, usually neurologic o rarely, gastrointestinal, are uncommon at effective do levels.[54,59,60] However, induction of polymorphic VT h been reported in the absence of QT prolongation,[63] an in 1 series the incidence in patients with a history recurrent VT/VF was 11%.[64]

Flecainide

Flecainide is a potent class I agent with some add tional effects consistent with class III activity. In vit studies have shown delayed repolarization in canin ventricular muscle, and significant prolongation of i tracardiac monophasic action potentials occurs man.[65] Flecainide produces concentration-related i creases in PR, QRS and QT intervals[66] and prolongs t ventricular effective refractory period.[67] No major h modynamic changes have been found with antia rhythmic oral doses,[66] but minor negative inotrop effects occur during intravenous infusion.[68]

Flecainide produces marked suppression of ventri ular arrhythmias. In a dose-ranging study in 11 patien with refractory chronic arrhythmias, 8 with recurre VT, oral flecainide produced total suppression of VP in 6, (97% suppression overall) and total suppression VT during the initial evaluation. Effective plasm concentrations ranged from 245 to 980 ng/ml with dos of 100 to 300 mg every 12 hours. Nine patients continue to have substantial arrhythmia suppression during 1 11 months (mean 6.6) of continued therapy.[66] Oth short- and long-term studies with oral flecainide ha produced similar findings.[69–71]

Flecainide is well absorbed after oral administratio and has a long plasma half-life[66] (Table II). Adver effects appear to be minor (dizziness and blurring vision) and infrequent with oral doses that produce si nificant arrhythmia suppression.[65,69,70] Transient di

ziness and circumoral paresthesia have been reported after intravenous administration.[66] In 1 study, a paradoxical increase in arrhythmia frequency was noted in 4 of 11 patients shortly after starting and after withdrawing oral flecainide;[66] QT prolongation with induction of VT has also been reported.[72]

Lorcainide

Lorcainide is a local anesthetic that reduces action potential duration, but prolongs the effective refractory period. In man, lorcainide prolongs PR and QRS intervals, slowing intraventricular conduction dose-dependently.[73] Accessory pathway conduction and refractory periods are also prolonged and depression of sinus nodal function has been reported in sinoatrial disease.[74] Oral lorcainide produces little hemodynamic effect, but moderate negative inotropic effects have been reported with intravenous administration.[75]

Lorcainide is a potent antiarrhythmic, with activity against supraventricular as well as ventricular arrhythmias.[73,76] In 1 study in 10 patients with chronic ventricular arrhythmias, lorcainide (100 mg every 12 hours) produced 82 ± 20% VPC suppression compared with placebo.[77] In other studies, 9 of 15 patients had "significant" VPC suppression after intravenous doses chosen to give plasma concentrations of 200 or 300 ng/ml;[78] total suppression of recurrent VT/VF resistant to other drugs occurred in 6 of 7 patients given 100 mg every 8 to 12 hours.[79] In 20 patients treated for 6 months during recovery from MI, arrhythmia suppression appeared to increase progressively, with a 92% reduction overall at the end of the study.[80]

Lorcainide shows high hepatic clearance and saturable presystemic elimination, the bioavailability increasing with increasing oral dosage. It is extensively distributed and the half-life is variable (mean about 8 hours) (Table II).[81] One metabolite, norlorcainide, has antiarrhythmic activity and a half-life of approximately 20 hours.[82] Norlorcainide levels are low after short-term intravenous administration,[78] but significant accumulation occurs after repeated doses and plasma levels eventually exceed those of the parent drug.[77] Optimal plasma concentrations for lorcainide are poorly defined and presumably vary with metabolite accumulation, but levels of 150 to 400 ng/ml are considered "therapeutic."[78,82] Oral dosage can be given twice daily.[77] Neurologic and gastrointestinal adverse effects are common at the start of treatment and sleep disturbances (vivid dreams) also occur frequently.[77,78]

Discussion

Electrophysiologic and antiarrhythmic effects: All of the above agents have class I antiarrhythmic activity, reducing the initial rate of increase (phase 0) of cardiac action potentials.[1] Their effects on other action potential characteristics vary, and a subdivision of the class has been proposed to take this into account.[83] In this scheme, class Ia agents are those with potent effects on phase 0, producing prolongation of action potential duration. Examples are quinidine, procainamide and disopyramide. Class Ib agents have less effect on phase 0 and tend to shorten action potential duration (lidocaine, tocainide, and mexiletine); class Ic agents have marked effects on phase 0 and produce little change in action potential duration (encainide, flecainide and lorcainide). The clinical value of this electrophysiologic classification remains to be established. The effects of individual drugs on the action potentials of different cardiac tissues vary considerably, and findings in 1 isolated preparation are unlikely to reflect total drug activity in the whole heart. In addition, active metabolites with electrophysiologic characteristics different from those of their parent drugs may be present in vivo (for example, encainide). Nevertheless, the subdivision does reflect some clinical differences between class I drugs. Class Ic agents produce striking suppression of ventricular arrhythmias, at least in short-term studies, whereas class Ia agents seem less potent, and class Ib agents even less potent. In addition, class Ia and Ic agents show activity against a wider range of arrhythmias, including those of supraventricular origin. Unfortunately, the marked potency of class Ic and Ia agents also seems to parallel an ability to induce serious ventricular arrhythmias in some patients.

With the exception of tocainide and mexiletine, all of the newer agents produce increases in PR and QRS duration at antiarrhythmic plasma concentrations. These changes may be quite marked, and monitoring of QRS prolongation has been suggested as a means of optimizing dosage with encainide. Despite this, the development of significant heart block is uncommon. QT prolongation seems least likely to occur with the class Ib agents, and a number of studies[3,6] have documented QT shortening with tocainide.

Hemodynamic effects: Although experience of long-term oral therapy is limited with some of the newer agents, the hemodynamic effects of the drugs appear minor. Some negative inotropic effects occur after intravenous administration, and with lorcainide and tocainide, these appear to be related to the rate of administration as well as to the dose given. However, the long-term effects of the agents with active metabolites are not predictable on the basis of short-term intravenous exposure, and the hemodynamic effects of the active metabolites are largely unknown.

Pharmacokinetic properties: Pharmacokinetic properties play a particularly important role in determining the clinical value of antiarrhythmic drugs. Drug effects are generally related to plasma concentration; for safe long-term therapy, concentrations should be predictably related to dose and should be stable in the patient to avoid failure of therapy or toxicity. These are difficult goals to achieve, as antiarrhythmic drugs are used in a patient group with widely varying cardiac, renal and hepatic function. Multiple drug therapy, with the potential for drug interaction, is a frequent additional complication.

Some of the newer class I agents have pharmacokinetic properties (Table II) that may, in theory, be troublesome. The bioavailability of lorcainide and encainide is highly variable, and with lorcainide it is known to be dose-dependent. Absorption is likely to be un-

predictable, and increasing dosage may produce disproportionate increases in plasma concentration with unexpected toxicity. This may be less troublesome with encainide than with lorcainide because the ratio of toxic to effective encainide concentrations appears to be high.

Active metabolites contribute to the effects of lorcainide and encainide after repeated dosage. They may not make a major contribution at the start of treatment and, as a result, the effects of short- and long-term therapy may differ. Similarly, intravenous and oral therapy result in different metabolite concentrations initially, as the metabolites are generated more rapidly with oral therapy on "first pass" through the liver. Concentrations of active metabolites should be taken into account if plasma concentration monitoring is used to optimize dosage; at present, the quantitative effects and therapeutic ranges of these metabolites are poorly defined. Liver disease and drug inhibition or induction of hepatic microsomal enzyme activity may influence the formation of active metabolites and overall drug activity, but this area also remains to be investigated.

Many patients with arrhythmias have intrinsically unstable cardiac, renal or hepatic function. In theory, absorption and elimination of drugs with high metabolic clearance (such as encainide or lorcainide) may be altered in patients with liver disease and perhaps those with cardiac failure. Liver disease significantly impairs the elimination of the high-clearance drug mexiletine, although cardiac failure appears to have little effect. In contrast, tocainide elimination shows little change in chronic liver disease, but excretion is predictably impaired in patients with end-stage renal failure. Tocainide plasma concentrations are usually stable over long periods in patients with chronic arrhythmias, perhaps due to the availability of 2 routes of elimination (metabolic and renal), which compensate one another for day-to-day changes in excretory function. Cardiac failure appears to have little effect on tocainide disposition, and there is little binding to the $alpha_1$ acid glycoproteins that are known to alter the free fraction of lidocaine in acute MI.

All of the newer class I agents show prolonged activity after repeated dosage, allowing oral administration 2 to 4 times daily without the need for controlled-release dosage formulations. With encainide, continuous arrhythmia suppression with these dosage intervals relies on the accumulation of active metabolites with long half-lives, as the half-life of the parent drug is relatively short. Intravenous dosage forms are available for all the newer class I agents, although for those with long half-lives, complex loading regimens are necessary to achieve effective levels quickly and to avoid subsequent accumulation if intravenous administration is prolonged. With tocainide and mexiletine, combined oral and intravenous loading doses that circumvent this problem have been described for emergency use.[25,41]

Adverse effects: Dose-related neurologic and gastrointestinal adverse effects occur with all the newer class I agents, but with encainide and flecainide they appear to be minor and infrequent at dose levels that produce marked arrhythmia suppression. With the other agents, dose-related effects may be minimized by reducing the dose or rate of intravenous administration or by giving smaller doses more frequently. Serious adverse effects (agranulocytosis, pulmonary fibrosis, liver dysfunction and convulsions) have been reported with a number of agents, but are uncommon. Induction of ventricular arrhythmias can occur with all of the newer agents, although this phenomenon has been reported most frequently with encainide and flecainide.

Conclusions

The newer class I antiarrhythmic agents offer combinations of pharmacokinetic properties and electrophysiologic, antiarrhythmic and adverse effects that are different from those of the currently available drugs. None achieve the perhaps unrealistic goal of efficacy in all patients, complete freedom from adverse effects and appropriate pharmacokinetic properties for both intravenous and oral use. Encainide and flecainide are extremely potent and usually well tolerated, but their potency may carry a risk of arrhythmia induction. Dose-related neurologic and gastrointestinal adverse effects are common with the other agents, but more serious toxicity appears to be rare. Tocainide appears to have useful pharmacokinetic properties for predictable long-term use in a variety of different patient groups.

No two arrhythmias are the same, and no antiarrhythmic drug can be expected to suppress all arrhythmias, irrespective of underlying mechanism or etiology. Similarly, no drug can be expected to behave ideally in all patients, irrespective of age, clinical condition and other drug therapy. Faced with this degree of individual variation, there is clearly a need for more antiarrhythmic agents, each differing subtly in electrophysiologic effects and pharmacokinetic behavior. The newer class I agents are a step toward fulfilling this need and, by providing new combinations of properties, increase the options for individualization of therapy in the high-risk patient.

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Effect of Antiarrhythmic Drugs on Mortality After Myocardial Infarction

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The theoretical potential for a preventive or prophylactic effect of antiarrhythmic drugs (excluding beta blockers) in the treatment of coronary patients with ventricular arrhythmias has not been realized. Randomized controlled clinical trials conducted during the early hospital phase after an acute myocardial infarction as well as after discharge have not demonstrated an effect on patient survival.

Three possible explanations exist. First, treatment of ventricular arrhythmias does not improve prognosis. Although this explanation is supported by the overall trial results, it is contrary to massive evidence from animal, clinical and epidemiologic studies. Second, treatment of ventricular arrhythmias does prolong life but benefit has not been observed in the trials. Limitations in applied methods, including insufficient sample sizes, may have obscured a true favorable intervention effect. Third, control of ventricular arrhythmias helps some patients but harms others. Concomitant treatment with digitalis and diuretics and, possibly, arrhythmogenic properties of the investigational drugs themselves might have confounded the overall results.

The second in particular, but also the third explanation, are the most plausible. Only 1 of the 20 controlled clinical trials considered for this review required presence of ventricular arrhythmias as an entry criterion. All trials were small; the largest number of patients enrolled in a single trial was 610 and the highest number of deaths in a trial was 49.

To resolve the uncertainty, increased attention to methodologic issues, such as selection of appropriate study populations, intervention strategies and larger sample sizes, is required. Only then will it be possible to determine whether antiarrhythmic drugs exert a life-prolonging effect.

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Ventricular arrhythmias are a major cause of death in patients with coronary heart disease. Electrocardiographic monitoring has enabled recognition and treatment of ventricular arrhythmias by a spectrum of agents that are more or less effective in controlling various rhythm disturbances. By suppressing the arrhythmias, these drugs can reduce symptoms associated with ventricular arrhythmias and, in addition, have the theoretical potential of preventing sudden arrhythmic deaths. This report critically reviews the evidence accumulated to date regarding the effect of antiarrhythmics on mortality, excluding beta-blocking agents in patients with myocardial infarction (MI).

Methods

This review considers clinical trials reported before March 1, 1983, in patients with a documented or suspected MI. Trials were included if they met the following criteria: (1) a total sample size of ≥100 enrollees, (2) random assignment of subjects to either a treatment or a control group, and (3) reporting of all-cause mortality.

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These criteria were chosen for important reasons. First, they were selected to limit this review to those trials that could possibly have had sufficient statistical power, as judged by sample size, to discern a clinically important benefit or trend. Moreover, a selection of a much larger number would have limited the review to very few trials. It is realized that a sample size in the thousands is often needed in a prevention trial to expose a treatment to a fair test. Many of the reviewed trials were not designed primarily to ascertain a drug effect on mortality. Second, the criteria were chosen to restrict the review to trials that incorporated randomization in their design, the best protection against treatment-allocation bias. Third, all-cause mortality was the preferred response variable to avoid the potential bias in determining cause-specific mortality. Total mortality data rely on a count without any element of judgment and allows straightforward comparisons across trials. Patients successfully resuscitated from ventricular fibrillation are not included among the deaths. As there is no available evidence that antiarrhythmic drugs favorably influence infarct size or exert a continued beneficial effect after treatment is terminated, only deaths that occurred during the defined intervention period are considered. To reduce the bias that may be introduced by differential withdrawal of patients in the analysis, all those randomized, regardless of level of compliance, have been included in the mortality estimates if the data were available. The exceptions

TABLE I Short-Term Trials of Antiarrhythmics: Design

Trial	Type Control	Type of Blind	No. Randomized	Intervention	Daily Dose	Entry Window (hours)	Length of Follow-up
Holmberg and Bergman[2]	Placebo	DB	104	Quinidine	1,200 mg	<24	2 weeks
Jones et al[3]	Placebo	DB	103*	Quinidine	1,200 mg	<24	3 days
Reynell[4]	Usual TX	Open	106	Procainamide	2–4 g	<96	2–4 weeks
Koch-Weser et al[5]	Placebo	DB	70*	Procainamide	2–4 g	<72	5–8 days
Jennings et al[6]	Placebo	DB	95*	Disopyramide	400 mg	<48	Hospital stay
Nicholls et al[7]	Placebo	DB	199	Disopyramide	600 mg†	<24	Hospital stay
Wilcox et al[8]	Placebo	DB	316	Disopyramide	450 mg	<24	6 weeks
Bennett et al[9]	Usual TX	Open	374*	Lidocaine, i.v.	0.5–1.0 mg/min†	<48	2 days
Pitt et al[10]	Dextrose	Open	222	Lidocaine, i.v.	2.5 mg/min†	<24	2 days
Darby et al[11]	Usual TX	Open	203*	Lidocaine, i.v.	2.0 mg/min†	<48	2 days
O'Brien et al[12]	Dextrose	DB	300	Lidocaine, i.v.	2.5 mg/min†	On admission	2 days
Lie et al[13]	Glucose	DB	212*	Lidocaine, i.v.	3.0 mg/min	<6	2 days
Valentine et al[14]	Saline	DB	364	Lidocaine, i.m.	300 mg	<12	2 hours
Lie et al[15]	Saline	DB	300	Lidocaine, i.m.	300 mg	<6	1 hour

* Randomized patients with unconfirmed myocardial infarction excluded in the reporting.
† Plus initial bolus of either 60 to 100 mg i.v. or 200 mg i.m.
DB = double-blind; i.m. = intramuscularly; i.v. = intravenously; TX = treatment.

TABLE II Short-Term Trial of Antiarrhythmics: Mortality Results

Trial	No. Randomized		No. of Deaths		% Mortality		
	Control	Intervention	Control	Intervention	Control	Intervention	p value*
Quinidine							
Holmberg and Bergman[2]	55	49	4	9	7.3	18.4	0.16
Jones et al[3†]	58	45	2	1	3.4	2.2	1.0
Procainamide							
Reynell[4]	55	51	5	5	9.1	9.8	1.0
Koch-Weser et al[5†]	33	37	3	3	9.1	8.1	1.0
Disopyramide							
Jennings et al[6†‡]	49	46	5	2	10.2	4.3	0.48
Nicholls et al[7]	99	100	12	10	12.1	10.0	0.80
Wilcox et al[8]	158	158	10	14	6.3	8.9	0.52
Lidocaine							
Bennett et al[9†]	125	249	3	15	2.4	6.0	0.20
Pitt et al[10]	114	108	4	6	3.5	5.6	0.68
Darby et al[11†]	100	103	5	7	5.0	6.8	0.81
O'Brien et al[12]	146	154	4	11	2.7	7.1	0.14
Lie et al[13†]	105	107	10	8	9.5	7.5	0.77
Valentine et al[14]	157	207	6	4	3.8	1.9	0.44
Lie et al[15]	153	147	0	0	0	0	...

* p values computed for chi-square test comparing the proportion of deaths in each group.
† Incomplete reporting.
‡ Treatment during coronary care unit stay, mortality reported only for the entire hospital stay.

consist of 7 trials that did not report the outcome in patients with unconfirmed MI. Therefore, for all these reasons the figures given are sometimes different from those in published trial reports.

The trials have been divided into short-term and long-term studies, the former having a treatment period of ≤2 months. In the short-term trials that met the review criteria, treatment was usually started at the time of hospital admission for a suspected MI and continued for up to 6 weeks. In the long-term trials treatment was initiated before hospital discharge and continued for 3 to 24 months.

The proportion of deaths in each treatment group has been compared by a chi-square test. This only approximates a comparison of survival curves, but the results are usually similar. To enable comparison of the different trials in this review, while taking into account differences in control group mortality rates, the effect of treatment has in each case been standardized to the relative difference. The approximate 95% confidence limits for the relative risk were computed by the Cornfield method.[1] One can reasonably conclude that the *true* effect of treatment in a particular trial lies somewhere within the bounds of the confidence limits given.

Results

Short-term trials: Fourteen acute-phase trials[2–15] met the review criteria (Table I). The total number of patients enrolled into the studies ranged from 104 to 374. Six trials[3,5,6,9,11,13] excluded in their reporting randomized patients with unconfirmed MI. Fixed oral dosages of quinidine (1,200 mg/day) and procainamide (2 to 4 g/day) were each evaluated in 2 trials[2–5] and disopyramide (400 to 600 mg/day) was evaluated in 3 trials.[6–8] The length of the treatment phase in the trials using oral administration varied from 3 days to 6 weeks. Seven trials of lidocaine, 5 using an intravenous infusion[9–13] and 2 a single intramuscular injection[14,15] fulfilled the criteria. An initial injection was given, followed by intravenous infusion at a rate of 0.5 to 3 mg/min. The

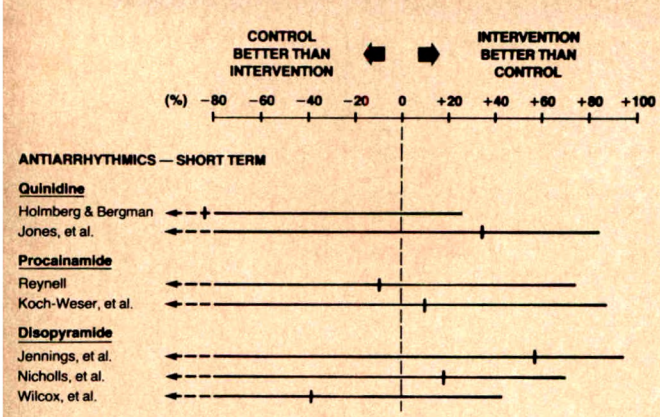

FIGURE 1. Estimates (**verticle bars on horizontal lines**) with approximate 95% confidence limits of the relative difference in total mortality between control and intervention in 7 short-term trials of oral antiarrhythmic drugs in the acute phase of myocardial infarction.

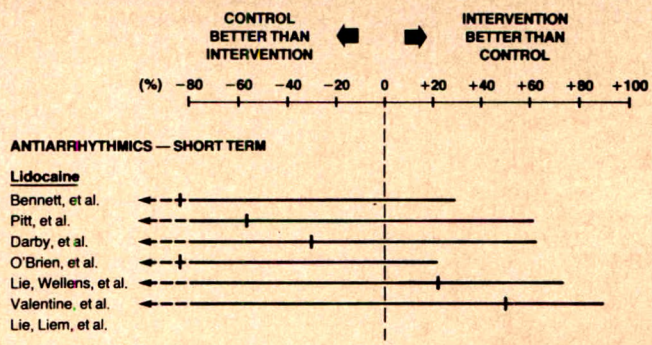

FIGURE 2. Estimates (**verticle bars on horizontal lines**) with approximate 95% confidence limits of the relative difference in total mortality between control and intervention in 7 short-term trials of lidocaine in the acute phase of myocardial infarction.

intramuscular dose was 300 mg. Ten of the 14 short-term trials used a double-blind design (Table I).

The mortality results are shown in Table II and Figures 1 and 2. The number of deaths was relatively small in all trials. In 4 of the 7 studies that evaluated oral treatment, the mortality rate was lower in the treatment group compared with the control group. In 3 trials (1 of each of the drugs tested) there were fewer deaths among the control subjects compared with the patients given antiarrhythmics. Four of the lidocaine trials had a higher percent mortality rate in the treatment group and 2 of the trials had a lower rate. In the seventh trial, no deaths occurred during the treatment period. In none of the 14 short-term trials did the mortality difference reach statistical significance.

Adverse effects were fairly common and necessitated termination of treatment in many patients. At the end of the treatment phase the proportion of patients not receiving drugs varied from 10 to 40%. The antiarrhythmic effect of the agents was not evaluated and reported in a uniform or standardized manner. The suppression of frequent or complex ventricular premature beats was judged as substantial in 5 trials[4–6,10,13] and moderate in 4.[2,3,7,8] The effect was uncertain in 3 studies,[9,11,12] and 2 trials[14,15] did not provide information on suppression of ventricular premature beats.

Long-term trials: Only 6 trials[16–22] fulfilled the review criteria (Table III). Their sample sizes were also small, ranging from 146 to 568 patients. Randomized patients with unconfirmed MI were excluded from the analysis in 1 trial.[18] Fixed dosages of phenytoin (300 to 400 mg/day) were tested in 2 trials,[16,17] tocainide (600 to 1,200 mg/day) in 2[18,19] and mexiletine (600 to 750 mg/day) in 1 trial.[20] The sixth trial[21,22] differs from all other trials of antiarrhythmic drugs in that the dosage of the drug (aprindine) was determined by the suppression of ventricular arrhythmias and ranged from 100 to 200 mg/day. The intervention phases lasted 3 to 24 months. Five of the 6 trials were double-blind (Table III).

Two of the trials showed a trend in favor of active treatment; 3 had a reverse trend and in 1 trial, the mortality rate was the same in the 2 groups (Table IV, Fig. 3). No differences were statistically significant.

By the time of trial termination, the proportion of patients not taking active drugs ranged from 20 to 30%. The suppression of frequent or complex ventricular premature complexes was considered substantial in 4 trials,[16,18,19,22] moderate in 1[20] and unknown in 1 study.[17]

TABLE III Long-Term Trials of Antiarrhythmics: Design

Trial	Type Control	Type of Blind	No. Randomized	Intervention	Daily Dose	Entry Window	Length of Follow-Up (mo)
Collaborative Group[16]	Low-dose phenytoin	DB	568	Phenytoin	300–400 mg	At hospital discharge	12
Peter et al[17]	Usual TX	Open	150	Phenytoin	Variable*	Before CCU discharge	24
Rydén et al[18]	Placebo	DB	112†	Tocainide	1,200 mg‡	2 days	6
Bastian et al[19]	Placebo	DB	146	Tocainide	600 mg	7–10 days	6
Chamberlain et al[20]	Placebo	DB	344	Mexiletine	600–750 mg	6–14 days	4 (3 mos intervention)
Van Durme et al[21]	Placebo	DB	300	Aprindine	100–200 mg§	11–16 days	12

* After initial loading doses, daily dosage adjusted to achieve plasma levels from 40 to 80 μmol/liter.
† Randomized patients with unconfirmed myocardial infarction excluded in the reporting.
‡ Plus initial loading dose.
§ Adjusted to achieve arrhythmia suppression.
CCU = coronary care unit; DB = double blind; TX = treatment.

TABLE IV Long-Term Trial of Antiarrhythmics: Mortality Results

Trial	No. Randomized		No. of Deaths		% Mortality		
	Control	Intervention	Control	Intervention	Control	Intervention	p Value*
Collaborative Group[16]	285	283	26	23	9.1	8.1	0.75
Peter et al[17]	76	74	14	18	18.4	24.3	0.49
Rydén et al[18]	56	56	5	5	8.9	8.9	1.0
Bastian et al[19]	74	72	3	4	4.1	5.6	0.97
Chamberlain et al[20]	163	181	19	24	11.7	13.3	0.78
Hagemeijer et al[22]	149	151	18	11	12.1	7.3	0.25

* p values computed for chi-square test comparing the proportion of deaths in each group.

In summary, 20 randomized controlled clinical trials of antiarrhythmic drugs in MI patients who met the review criteria have been published. The effect of 8 different agents on mortality was evaluated. More than 4,500 patients were enrolled into the trials and the outcome of the treatment was reported.

One would have expected 1 trial to have reached a p value of <0.05 by chance alone, but a statistically significant benefit was not observed in any trial. In fact, favorable and nonfavorable trends were equally common among the 20 trials.

Discussion

As in any clinical trial in which no statistically significant difference is observed, 3 explanations are possible. In the case of antiarrhythmics these are (1) control of ventricular arrhythmias with the agents used does not improve prognosis, (2) control of ventricular arrhythmias with these agents prolongs life, but this prolongation was not observed in the trials, and (3) treatment of ventricular arrhythmias with these agents helps some patients but harms others.

Control of ventricular arrhythmias does not improve prognosis: The findings from the reviewed trials support the explanation that control of ventricular arrhythmias does not improve prognosis. Although the trials were small, one would have expected that if control of ventricular arrhythmias prolongs life, more than half of the trials would show a trend in favor of active treatment.

On the other hand, research data reviewed in other reports in this symposium strongly support the view that suppression of ventricular arrhythmias should be beneficial. Moreover, extensive use of antiarrhythmic drugs among cardiac patients, which appears to be based on the clinical impression of many cardiologists, also is counter to the explanation that these drugs have no preventive effect.

Control of ventricular arrhythmias prolongs life but the prolongation was not observed in the trials: Limitations in the design and conduct of the reviewed trials could be used to argue the explanation that control of ventricular arrhythmias prolongs life, although this effect was not observed in the trials. The patient selection was less than optimal. In 19 of the 20 trials, patients were enrolled whether or not they had ventricular arrhythmias. Patients with no demonstrable arrhythmia probably would not benefit substantially from antiarrhythmic treatment. This subset of patients would tend to dilute any benefit of treatment in patients with ventricular arrhythmias.

The trials were too small. Only 1 involved >400 patients.[16] A properly designed prevention trial of antiarrhythmic drugs requires a total sample size of at least 1,000. The size is dependent on the mortality rate; that is, the higher the rate the smaller sample size needed.

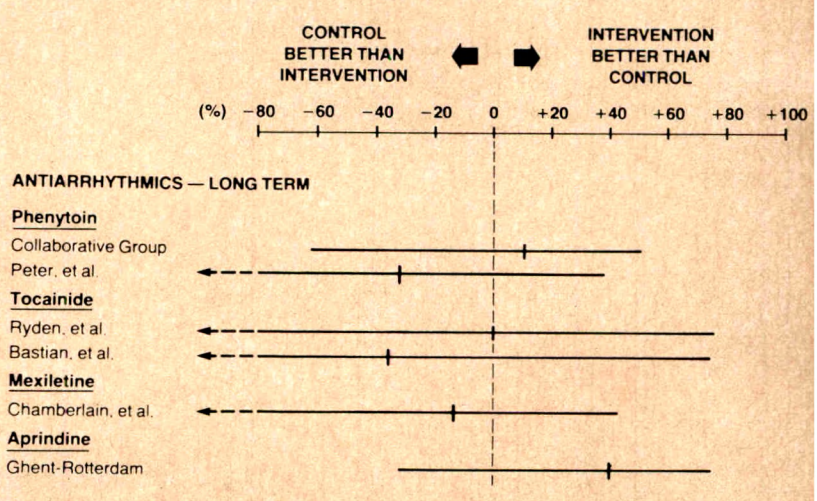

FIGURE 3. Estimates (**verticle bars on horizontal lines**) with approximate 95% confidence limits of the relative difference in total mortality between control and intervention in 6 long-term trials of antiarrhythmics of post–myocardial infarction patients.

The intervention programs in the reviewed trials were less than optimal. Nineteen of the trials used a fixed dose for each participant. In only 1 was the dosage adjusted based on arrhythmia suppression.[21,22] All trials evaluated a single drug. Thus, the programs are different from clinical practice, in which dosage is adjusted to achieve control of ventricular arrhythmias, and if 1 drug fails, many others are tested. It is not surprising that the effect of treatment on ventricular arrhythmias was moderate to uncertain in almost half of the trials that reported results on control of ventricular arrhythmias.

Adverse effects of treatment were very common and often led to treatment withdrawal. In the 13 trials of oral drugs (excluding the 7 lidocaine studies), about one fourth of the patients were not taking active oral treatment at the end of the trial.

All these factors indicate that the effect of antiarrhythmic drugs has not been fairly tested. Better attention should be given to certain features of study design. The trials should be limited to patients with known ventricular arrhythmias. Larger numbers of patients need to be studied. The objective of the trial should, as much as possible, mimic good clinical practice and examine whether arrhythmia control has a life-prolonging effect. For example, a patient who does not respond to a first (modest) dose of a drug ought to receive a higher dose and, if this is not effective, a second drug.

Treatment of ventricular arrhythmias helps some patients but harms others: Recent evidence suggests that antiarrhythmics may induce or worsen existing ventricular arrhythmias in 10 to 15% of patients.[23] This might be even more frequent in patients who receive digitalis or diuretics or both.[24,25] This explanation is difficult to prove. However, in future trials, special attention should be given to drug-induced arrhythmias, and the use of digitalis and diuretics should be closely monitored.

Conclusion: The first explanation—ineffectiveness of the drugs—appears to be the least likely. The second appears the most plausible, as all reviewed trials had severe limitations. The third explanation is difficult to reject until we know more about the intrinsic arrhythmogenic property of antiarrhythmics. Increased attention to methodologic issues will be necessary in future trials. Only then will it be possible to determine whether antiarrhythmic drugs exert a preventive effect on mortality.

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Methods for Documenting Antiarrhythmic Efficacy

DONALD C. HARRISON, MD

Methods of documenting the efficacy of antiarrhythmic drugs are controversial because of wide inter- and intrasubject variability of the arrhythmias treated. In patients with symptomatic arrhythmias, clinical benefit can be inferred when symptoms are reduced or abolished, but the response cannot be quantitated. Multiple ambulatory monitoring periods before and during treatment permit determination of reductions of arrhythmia to levels of statistical significance but are costly and time-consuming.

Programmed electrophysiologic induction study may be helpful in determining efficacy of some antiarrhythmic agents because of its high specificity, but its use is limited because of a low sensitivity. Titrating patients with multiple dosing into accepted plasma level therapeutic ranges may be helpful for individual patient care but does not allow quantitation. Recently, a statistical model based on linear regression analysis with established 95 and 99% confidence intervals has been used to compare efficacy of quinidine and encainide with success. Wider application of this model is suggested for determining antiarrhythmic drug efficacy.

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Clinical studies to establish therapeutic efficacy and to determine the relation between plasma concentrations of antiarrhythmic drug and effect are often performed in small groups of patients, frequently with inadequately designed studies. Therefore, questions remain about the basic approach for documenting individual and group antiarrhythmic efficacy for this class of agents.[1] Thus, the question of study type and design for demonstrating efficacy continues to be a major problem for the cardiologist/investigator.

A major problem results from spontaneous variation in the occurrence of individual ventricular premature complexes (VPCs) and of the more complex forms such as runs, couplets, bigeminy, trigeminy and the R-on-T phenomenon. Studies by Winkle[2] and Morganroth et al[3] demonstrated the wide range of variability for the occurrence of simple and complex VPCs in patients with heart disease. These investigators proposed methods that utilize multiple ambulatory monitoring periods that can provide data to document the efficacy of antiarrhythmic drugs. Other problems result from the use of electrophysiologic studies inducing recurrent ventricular tachycardia (VT) and determining which antiarrhythmic drug prevents such induction. As increasing sophistication and complexity of electrophysiologic study have been proposed to document the efficacy of drugs when administered for long periods, its use for the short-term evaluations of new antiarrhythmic drugs has become more limited.[4–6] Moreover, blood levels for the effectiveness of antiarrhythmic drugs and therapeutic indexes have been established by careful in-hospital control studies and carefully defined patient groups for some agents, but have not been evaluated as methods for establishing efficacy in ambulatory outpatients.[7–9] Other approaches using new biostatistical methods of linear regression analyses with the establishment of confidence intervals for homogenous patient groups have also been presented as means for determining the antiarrhythmic efficacy of a given drug.[10] These approaches have been criticized because they cannot be generalized to nonhomogenous patient groups nor to those who were not participants in developing the linear regression analysis as opposed to group responses.

Therefore, this report outlines the present state of knowledge with each of these approaches and provides the clinical investigator with a rationale for choosing 1 approach rather than another when confronted with studies relating to the use of a new antiarrhythmic agent. Considerable controversy has been expressed for each approach by specific proponents of an alternate approach during the past several years. An attempt is made to put each of these methods into clinical perspective.

Symptomatic Arrhythmias

For arrhythmias that present with clear-cut symptoms, such as syncope, hypotension and the appearance of symptomatically troublesome ectopic beats noted by

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the patient, it seems likely that drugs that alleviate these symptoms or markedly reduce them might be judged as effective. This may be true for patients who are good observers or the ones who have severe, highly symptomatic, life-threatening, recurrent VT. However, symptomatic arrhythmias occur in only a small group of such patients on a regular basis. The symptoms frequently do not correspond to periods in which objective documentation of the arrhythmia has occurred, and few patients are good observers. This approach will not lend itself to objectivity and a likelihood of demonstrating efficacy to a regulatory agency. For this reason such approaches have not been taken by most investigators who attempt to document the effectiveness of antiarrhythmic drugs during the past decade.

Use of Ambulatory Arrhythmia Monitoring

With the advent of 24-hour ambulatory monitoring, it became exceedingly easy to document that many patients have ectopic VPCs.[1] These have been documented with various degrees of frequency and varying degrees of complexity in patients with heart disease.[11] Clearly, by establishing entry criteria, one can choose patients to enter major drug protocols who have a high level of ventricular arrhythmia. However, because of marked spontaneous variability,[2,3] the degree to which suppression of such arrhythmias must be documented with the administration of antiarrhythmic drugs makes these techniques for the study of drugs difficult. They frequently lead to high levels of ≥60 VPCs required for entry into a study. Depending on the number of pretreatment recordings and the number of recordings once the patient is receiving established antiarrhythmic drug therapy at steady-state levels of the compound, varying degrees of reduction in VPCs are required for documenting efficacy.[2,3] In general, with 2 recordings before and 2 recordings during treatment, a 75% reduction is considered to be significant. Many drugs, such as beta-blockers and some of the class I antiarrhythmic drugs, do not reduce arrhythmias more than this; therefore, their documentation using ambulatory monitoring is difficult.

In addition, these approaches are costly and, because they require establishing a threshold for entering into a study, most patients will have high levels of ventricular ectopic activity or be in a period in which they are in the peak of their cycle for spontaneous variability. The patients at the nadir of their spontaneous variability are unfortunately excluded from study when they do not achieve the threshold and later may have a much greater frequency of ectopic rhythms and complexity. Using these techniques for a threshold determination before entry will bias most studies into showing efficacy for an agent.

Although spontaneous variability of VPCs in individual patients makes determination of individual response and efficacy difficult, group responses can be used to assess efficacy over short time intervals.[2,12] When group data without treatment are compared for several different monitoring intervals separated by time, there is a remarkable comparability of the number and frequency of VPCs for the groups.[12] Thus, reduction in the average VPCs in such a patient group can be used to judge antiarrhythmic efficacy.

Electrophysiologic Studies for Drug Efficacy

Program stimulation by electrophysiologic methods to produce a prototype arrhythmia that has been observed in a patient under spontaneous conditions has become a standard method of examining the efficacy of antiarrhythmic drugs. Such programs are discussed in greater detail in Ruskin's report in this present symposium. Although initially these techniques appeared promising,[4–6] several problems have arisen. First, such techniques require hospitalization and electrophysiologic study in a sophisticated laboratory. Because of their cost and risk to patients, they can be used in only those patients who have already experienced a life-threatening arrhythmia. For most investigators, this has required documentation of sustained VT or ventricular fibrillation (VF). Second, as attempts have been made to make electrophysiologic testing more specific, more complex and sophisticated protocols have been introduced. The use of 3 programmed premature stimuli and the use of intravenous infusions of catecholamines have helped to increase the specificity of the tests but have markedly limited their sensitivity for detecting the efficacy of an antiarrhythmic drug. A single drug frequently cannot be demonstrated to be efficacious against electrophysiologic induction in >15% of patients. Combined drugs may reach levels in the 30% range for efficacy. Electrophysiologic study with programmed stimulation to produce a prototype arrhythmia and then to determine which antiarrhythmic drug prevents the reinduction of the arrhythmia has been used to determine the efficacy with increasing frequency in the past 5 years.

In addition, a drug could be highly effective in preventing recurrences of life-threatening arrhythmias without preventing induction. This has been demonstrated for amiodarone, encainide and lorcainide.[13,14] Finally, I suggest that different end points other than preventive induction of VT might be considered for these tests. These studies are not helpful in many of the patients with less-than-life-threatening arrhythmias and are not generally used in these patients.

Blood Level Determinations for Therapeutic Effect

For several antiarrhythmic drugs, the therapeutic effective blood level has been well established in group studies.[7–9] New methods such as gas chromatography, high-pressure liquid chromatography, mass spectrometry and immunoassay for antiarrhythmic drugs have permitted their easy detection in plasma. Thus, it might be possible to establish therapeutic ranges for the efficacy of several of these drugs and simply use the observation that establishing a plasma level in patients within the therapeutic range might markedly reduce the occurrence of arrhythmias. Such studies fail to take into account the individual patient variability that has been noticed when the patients are under intense study in

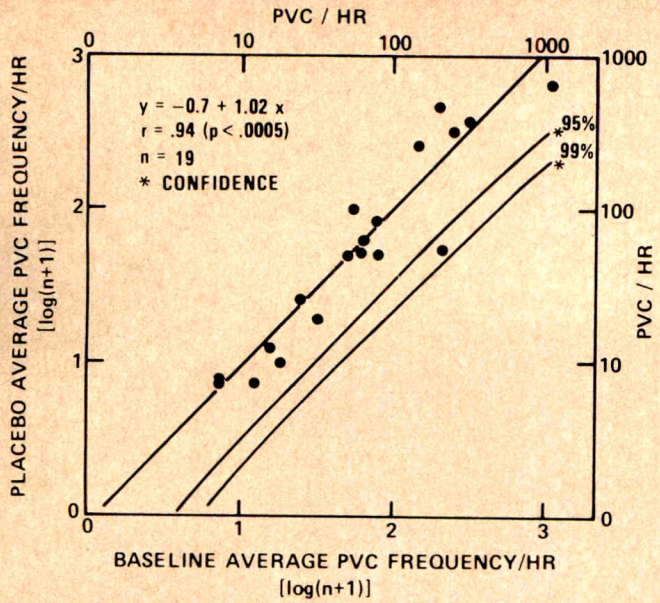

FIGURE 1. Demonstration of linear regression analysis with 95 and 99% confidence intervals of variability for baseline and placebo observations of the average frequency of premature ventricular complexes (PVCs) per hour of ambulatory electrocardiographic recordings. The analysis was performed on log (PVC frequency + 1) with corresponding absolute values on the opposite scale. The 95 and 99% confidence lines represent the 1-tailed confidence intervals for individual data points. Reproduced from Sami et al[10] with permission of the publisher.

clinical research units. Thus, this technique may not be helpful in determining individual patient responsiveness under different clinical conditions, especially in those in ambulatory outpatient settings.

Statistical Models Based on Linear Regression Analysis

To develop standards for distinguishing efficacy of antiarrhythmic drugs from spontaneous variability of VPCs, a new statistical approach was applied in 21 patients and was used to compare the response with 2 antiarrhythmic drugs by our group at Stanford.[10,15] Patients underwent ambulatory monitoring and exercise testing before and during 2 weeks of placebo therapy. A linear regression analysis was used to describe the relation between baseline and placebo VPC frequency and to set 95% and 99% 1-tailed confidence intervals for the relation (Fig. 1).[10]

The lower limits of baseline of VPC frequency for which this analysis could distinguish a placebo from true drug response was 2.2 VPCs/hour for ambulatory monitoring and 1.2 VPCs/min of exercise testing. To establish efficacy with 95% confidence, the minimal percent reduction of VPCs between baseline and placebo visits was 68% for treadmill testing and 65% for ambulatory monitoring.[10] The shortcomings of this technique are that new standards must be developed in homogenous patient groups to be studied with a particular agent, and that several ambulatory monitoring and treadmill sessions are required. Despite these problems, we believe the method has wide adaptability and should be further assessed.

Clinical Perspectives for Documenting the Effectiveness of Antiarrhythmic Drugs

When considering the various methods of documenting the effectiveness of antiarrhythmic drugs, several considerations for the clinician become apparent. Initially, it should be determined whether or not the approach is to demonstrate effectiveness in an individual patient or in a group of patients with a similar disease process. Based on these considerations, a rational approach can be developed.

For patients on an individual basis, 3 approaches seem relevant. First, for patients who have symptomatic ventricular arrhythmias either resulting in syncope or the detected presence of multiple VPCs, the abolition of symptoms with the administration of an antiarrhythmic drug in those patients who are careful observers appears to be a rational approach.

Second, when using multiple ambulatory monitorings before and after the administration of an antiarrhythmic drug, it seems feasible to use a 75% reduction in either complex forms or in the absolute frequency of VPCs as an endpoint for documenting the efficacy in a given patient. Whether or not reduction of this degree will reduce the prevalence of sudden death in this patient population has not been determined. Because only 1 episode of VF or sustained VT is necessary to result in death, it is problematic whether reductions of 75% in complex forms and in VPCs can be used as documenting efficacy in a given patient, particularly if death is the endpoint used and it occurs with a single episode of VF. This question can only be answered after further study.

Finally, an approach to administer the drug so that the patient's plasma concentration falls within a range that has been previously established by careful clinical investigation seems rational. Documenting that the peak and trough of the plasma concentration curve based on long-term administration all fall within the established therapeutic range for the given agent might be considered as establishing efficacy for a given patient. No studies have been successful in documenting this approach, although it was used to establish drug levels in the Beta-Blocker Heart Attack Trial[16] with a successful reduction in total and sudden cardiac deaths.

The approach to documenting antiarrhythmic drug efficacy in groups of patients with homogenous disease who have similar arrhythmias appears much more straightforward. By using ambulatory arrhythmia monitoring before and after administration of an antiarrhythmic drug, a rational approach should be possible. Patients in groups of 20 or more with homogenous disease processes have day-to-day variations in the average frequency of arrhythmias that are slight when averages for the group are utilized. Thus, a statistical reduction of even 25 or 30% in a group of patients should be sufficient to demonstrate that the drug has some degree of efficacy. It has been argued that reductions >70% in patients having ≥60 VPCs/min should be taken as clear-cut evidence of antiarrhythmic efficacy. The level of reduction of overall VPCs to document efficacy for such study protocols has not been defined and it seems

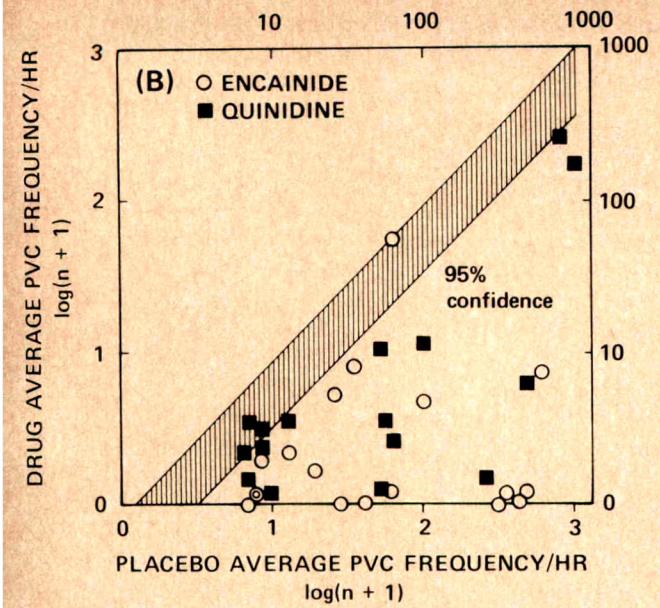

FIGURE 2. Responses of patients to encainide and quinidine. The shaded area represents the 95% confidence level from Figure 1. To distinguish true drug response from placebo effect at 0.05 level of significance, the single point that describes the placebo and postdrug responses must fall below the 95% confidence limit. The higher the average frequency of premature ventricular complexes (PVCs) during placebo therapy, the lower the percent reduction required to establish drug efficacy at a given confidence interval. Reproduced from Sami et al[15] with permission of the publisher.

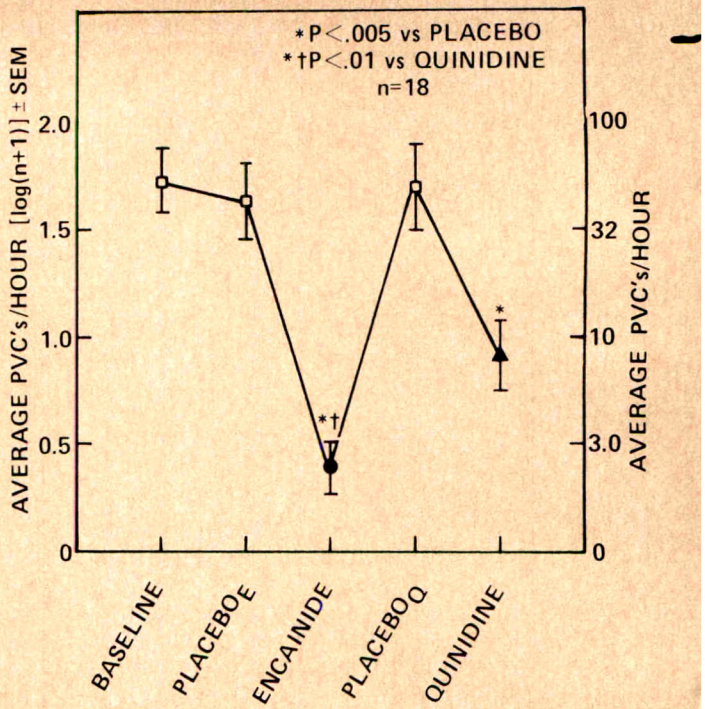

FIGURE 3. The means and standard errors of the mean for the average hourly frequency of premature ventricular complexes (PVCs) on ambulatory monitoring for each of 5 visits is shown. Paired *t* tests were used to compare the response to each drug with the prior placebo response and with the response to the other drug. Placebo$_E$ is that preceding encainide; placebo$_Q$ is that preceding quinidine. SEM = standard error of the mean. Reproduced from Sami et al[15] with permission of the publisher.

likely this reduction of total VPCs might not indicate whether or not sudden arrhythmic death would be reduced.

A much more rational approach, in my opinion, is the use of ambulatory monitoring twice before administering an antiarrhythmic drug and the establishment, by linear regression analyses, of the relation between a response with a placebo and with an entry ambulatory monitoring. Establishing by biostatistical means the 95 and 99% confidence intervals becomes possible. Thus, the administration of a drug to a group of patients that falls within such a homogenous disease process can demonstrate efficacy.[10,15] Such approaches have been documented with encainide and quinidine in our laboratories (Fig. 2 and 3). It has also been possible to establish that encainide is more effective than quinidine in reducing such arrhythmias both during ambulatory monitoring and in exercise testing.[15] This approach has great promise for studying the efficacy of antiarrhythmic drugs in groups of patients with complex and frequent ectopic rhythms. This method should gain more widespread use for clinical research protocols in the future. Other new approaches that would have wide applicability should be sought.

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Role of Electrophysiologic Techniques in the Selection of Antiarrhythmic Drug Regimens for Ventricular Arrhythmias

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Programmed electrical stimulation of the heart provides a useful new technique for guiding the selection of antiarrhythmic drug regimens in selected patients with ventricular tachycardia (VT) or ventricular fibrillation. The technique of programmed electrical stimulation has been applied successfully in patients with recurrent sustained VT, out-of-hospital ventricular fibrillation and unexplained syncope in the presence of structural heart disease. The complete suppression of VT induced by programmed electrical stimulation by a drug regimen is highly predictive of freedom from both recurrent VT and sudden death. In addition, this technique may hold promise as a means of assessing the arrhythmogenic effects of antiarrhythmic drugs in selected patients.

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The use of programmed electrical stimulation of the heart in conjunction with intracardiac electrographic recordings has contributed importantly to our understanding of the mechanisms of ventricular tachyarrhythmias and has enhanced our ability to examine objectively the efficacy of therapeutic interventions in modifying or preventing their occurrence. In assessing the value of programmed stimulation techniques in the management of patients with ventricular arrhythmias, the following issues will be addressed: the sensitivity and specificity of tachycardias induced by programmed electrical stimulation, the safety and practicality of serial pharmacologic-electrophysiologic testing techniques, the reproducibility of responses to antiarrhythmic drugs during serial electrophysiologic testing, and the predictive value of programmed electrical stimulation in selecting long-term antiarrhythmic drug regimens.

Lown et al[1] proposed the hypothesis that the suppression of ventricular premature beats, particularly repetitive forms, serves as a reliable endpoint to guide the selection of drug regimens aimed at preventing life-threatening ventricular tachyarrhythmias. This approach relies upon the use of both ambulatory and exercise electrocardiography to assess patients' baseline arrhythmias without drugs, as well as responses during short- and long-term antiarrhythmic drug testing. The results of this approach in properly selected patients (such as in those with frequent spontaneous arrhythmias) are encouraging.[2] However, there exist important limitations to the use of ventricular ectopic activity as an endpoint for the selection of antiarrhythmic drug therapy in patients with life-threatening ventricular arrhythmias. Even complex forms of ventricular ectopic activity may be detected in patients at low risk for sudden death, raising significant questions about the specificity of this finding.[3–5] In some patients in whom ventricular ectopic activity does occur, marked variation in complexity and frequency of ventricular ectopic activity may be seen when the results of several monitoring periods are compared.[6–8] Such variability may, in some instances, be so great as to mimic a drug effect. Another problem arises from the fact that freedom from spontaneous ventricular ectopic activity seems not be a highly specific indicator of protection against ventricular tachycardia (VT) or ventricular fibrillation (VF). We have observed that 15 to 25% of patients resuscitated from an episode of VT or VF subsequently may be found to be free of significant ventricular ectopic activity during ambulatory monitoring. Therapy for such patients is impossible to evaluate using suppression of ventricular ectopic activity alone. In other studies, investigators have also demonstrated a potential for dissociation between the prevention of spontaneous or electrically inducible VT and the suppression of ventricular ectopic activity by both pharmacologic and nonpharmacologic therapy.[9,10]

These limitations led several groups to seek alternative and potentially more reliable measurements to

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TABLE I Electrophysiologic Testing for Ventricular Arrhythmias—Massachusetts General Hospital Protocol

A. Withhold antiarrhythmic drugs (≥5 half-lives) under continuous electrocardiographic monitoring
B. Baseline electrophysiologic evaluation without antiarrhythmic drugs
   1. Sinus nodal function studies
   2. AV nodal and His-Purkinje system conduction times and refractory periods
   3. Programmed PVS to test for inducible VT or VF
      a. Single (V_1V_2) and double ($V_1V_2V_3$) PVS during NSR and RV pacing at 3 drive cycle lengths (600, 500 and 400 ms) from RV apex. If no VT or VF induced →
      b. Triple ($V_1V_2V_3V_4$) PVS during NSR and RV pacing* (3 drive cycle lengths) from RV apex. If no VT or VF induced →
      c. Repeat (a) and (b) from RV outflow tract
      d. Adjuncts (rarely used):
         1. Isoproterenol infusion
         2. Left ventricular stimulation
C. Serial electrophysiologic-pharmacologic testing to define suppressive antiarrhythmic drug regimen.

* Triple PVS during RV pacing employed only in patients with clinically-proven spontaneous VT or VF.

AV = atrioventricular; NSR = normal sinus rhythm; PVS = premature ventricular stimulation; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

guide the selection of antiarrhythmic drug therapy. Early studies indicated that VT comparable in rate and morphology to that observed clinically could be initiated reproducibly by programmed cardiac stimulation in a majority of patients with a history of sustained ventricular tachyarrhythmias. After these initial observations, it became apparent that the use of sequential drug trials in conjunction with programmed cardiac stimulation would allow responses to individual drugs to be analyzed readily and in a highly reproducible fashion, thus providing an objective basis for the selection of long-term antiarrhythmic drug regimens in individual patients.[11–29]

Methods

The methods of electrophysiologic study used in this laboratory are outlined in Table I. The endpoint of programmed cardiac stimulation is the reproducible initiation of either sustained or nonsustained VT in response to some portion of the stimulation protocol. If sustained VT is induced, extrastimuli or bursts of rapid ventricular pacing are applied to interrupt the arrhythmia; sustained arrhythmias that result in angina or loss of consciousness are terminated with immediate asynchronous external electrical countershock.

The performance of baseline electrophysiologic studies in the absence of antiarrhythmic agents provides a reliable and consistent standard by which the efficacy and adverse electrophysiologic effects of antiarrhythmic drugs may be objectively assessed. In addition, a subset of patients with a history of spontaneous VT or VF will have no inducible arrhythmia at initial testing in the absence of drugs.[30] Serial antiarrhythmic drug testing without the benefit of baseline electrophysiologic observations without drugs will mask such patients and may, in some instances, obscure the fact that an antiarrhythmic agent either precipitated or exacerbated their spontaneous arrhythmias. Furthermore, preliminary logistic regression analysis of patients with VT or VF studied in our laboratory reveals that the results of initial electrophysiologic studies in the absence of drugs is an important predictor of the degree to which subsequent serial testing will achieve suppression of an inducible arrhythmia. In our patients, 77 and 73% of patients in whom nonsustained VT or VF, respectively, were induced achieved complete suppression of inducible arrhythmia during serial drug testing, whereas only 53% of patients whose baseline study revealed inducible sustained VT achieved suppression during subsequent drug testing (unpublished observations).

Sensitivity and specificity of induced arrhythmias: Some investigators have considered the initiation of "repetitive ventricular responses" of <5 beats to be a sufficient endpoint by which to assess antiarrhythmic drug efficacy during programmed stimulation protocols.[31,32] A repetitive ventricular response was originally defined as ≥1 nonstimulated premature ventricular depolarizations occurring reproducibly in response to a single stimulated premature ventricular depolarization delivered during sinus rhythm or atrial pacing. Greene et al[31] reported the induction of a repetitive ventricular response in 44 of 50 patients (88%) with a history of recurrent VT and in none of 12 control patients, suggesting that the induction of a repetitive ventricular response was a sensitive indicator of ventricular electrical instability and that the acute suppression of repetitive ventricular responses by drugs was a useful indicator of long-term antiarrhythmic efficacy. However, Ruskin,[33] Mason,[34] and their co-workers observed only a 15% incidence of repetitive ventricular responses in response to programmed single ventricular extrastimuli during sinus rhythm and atrial pacing in patients with recurrent VT or VF. This latter work indicated that repetitive ventricular responses induced in response to single ventricular extrastimuli during sinus rhythm or atrial pacing were an insensitive index of susceptibility to ventricular arrhythmias in patients with a history of life-threatening arrhythmias. In a later study by Farshidi et al,[35] repetitive ventricular responses that occurred after ventricular premature stimulation delivered during a paced ventricular drive had sensitivity and a specificity of 91%. Nacarelli et al[36] also determined that in patients with spontaneous VT, the induction of repetitive ventricular responses during ventricular pacing was more sensitive, although far less specific, than repetitive ventricular responses elicited during atrial pacing. Although a large prospective study by Livelli et al[37] using paced ventricular drives also found that the repetitive ventricular response had high sensitivity (92%), there was low specificity (57%) for detecting patients with previously documented spontaneous VT. Thus, the induction of a repetitive ventricular response is not a useful endpoint for defining antiarrhythmic therapy for patients with a history of ventricular tachyarrhythmias because of its low sensitivity when elicited during sinus rhythm or atrial pacing and its low specificity when elicited during ventricular pacing. In contrast, VT can be initiated by programmed cardiac stimulation in approximately 90% of patients with clinically documented, recurrent sustained VT related to coronary artery disease.[37,38] Furthermore, the specificity of VT initiated during programmed ventricular stimulation is extremely high, approaching 99% in the studies reported to date.[37,38] The sensitivity of programmed cardiac stimulation in patients with a clinical history of recurrent, nonsustained VT is somewhat lower, about 60%.[37,38] In patients with a clinical history of out-of-hospital VF we have found that VT or VF can be initiated reproducibly in approximately 75%.[22,39]

Serial drug testing: After a baseline study without drugs has been completed, antiarrhythmic agents are tested serially in selected patients for their ability to prevent initiation of VT by programmed cardiac stimulation. Standardization of electrophysiologic techniques and serial drug testing protocols

from one laboratory to another is presently lacking, rendering the interpretation and comparison of results of electrophysiologic-pharmacologic testing trials extremely difficult. In particular, some laboratories administer several parenteral agents in succession during the course of a day's testing, allowing for the accumulation of multiple antiarrhythmic drugs without adequate time for washout. Potential drug interactions may confound the findings at the time of electrophysiologic study in these patients and exclude a useful agent from consideration. For this reason, some centers, including our own, undertake serial testing only when steady-state serum drug concentrations have been achieved during long-term oral therapy and only after adequate washout of any previously administered antiarrhythmic drug has occurred.

Electrophysiologic testing of a drug during long-term oral therapy may be preferable to testing after the short-term intravenous administration of an antiarrhythmic agent. Variations in absorption and metabolism may contribute to electrophysiologic differences between testing after an intravenous loading dose and chronic oral therapy with the same agent.[40,41] Active metabolites of a number of drugs, including aprindine, lorcainide, procainamide, propranolol, verapamil and encainide, have been described, each of which may contribute to an agent's antiarrhythmic (or arrhythmogenic) potential. The clinical electrophysiologic effects of a drug are therefore better determined after several dosing intervals rather than a single intravenous loading dose or infusion. In addition, blood levels soon after intravenous loading may not reflect myocardial tissue levels. This is especially true of propranolol and quinidine, which concentrate in the myocardium after some delay.[40] Another advantage of studying patients while they are receiving a drug orally is that many of the potential side effects associated with a particular drug will be better and earlier appreciated.

The endpoint of serial drug testing is the complete suppression of inducible VT or VF by an antiarrhythmic drug. In a substantial percentage of patients, however, the goal of complete suppression of inducible arrhythmia cannot be achieved. Several investigators have commented on the ability of some antiarrhythmic agents to slow the rate of induced tachycardia, thereby rendering the patient less symptomatic during the arrhythmia and possibly allowing for the addition of pacemaker therapy to more effectively control recurrent tachycardias.[13,15,24,42,43] However, the efficacy of this approach has not been conclusively demonstrated. In addition, antiarrhythmic therapy may render a tachycardia more difficult to induce by programmed cardiac stimulation, requiring more aggressive modes of stimulation for initiation. The latter alteration may be predictive of the absence of recurrent spontaneous VT during long-term follow-up in patients in whom complete suppression cannot be achieved.[44]

We have observed that most antiarrhythmic drugs have an efficacy rate of about 25% during serial testing in patients with ventricular arrhythmias. Swerdlow et al[45,46] found that single agents averaged <15% efficacy, although these investigators used a more aggressive stimulation protocol. In addition, there was no statistically significant difference evident when the efficacy of various single agents was compared in their study.

Where single drugs are not effective in preventing the initiation of VT by programmed cardiac stimulation, a combination of drugs may be required. In our experience, 33% of patients have been discharged with at least 2 drugs after serial electrophysiologic testing, and 5% received 3 drugs. Caution is, however, recommended when combining 2 type I antiarrhythmic agents when neither drug alone has been successful in preventing the initiation of VT or VF. In 1 study, although induced VT was slower and better tolerated with a combination of 2 type I agents, in no case was the initiation of sustained VT prevented.[47] In our experience, the combination of a type IA drug such as quinidine with a type IB drug such as mexiletine has sometimes been effective when neither drug alone has effectively suppressed VT.

Adverse electrophysiologic effects of antiarrhythmic drugs: Antiarrhythmic drugs may exert a variety of unfavorable electrophysiologic effects in patients with ventricular arrhythmias. These effects include facilitation of induction of an arrhythmia, acceleration of the tachycardia rate, conversion of nonsustained to sustained VT or VF, and induction of nonclinical forms of VT. These adverse effects are observed frequently in the electrophysiology laboratory during serial antiarrhythmic drug testing. The precise clinical relevance of these effects has not been defined. We have found that some patients have both spontaneous and inducible VT in the presence of an antiarrhythmic drug and have no evidence of inducible VT in the absence of that drug.[22] In this subgroup of patients, we discontinue antiarrhythmic drug therapy and have observed no recurrent arrhythmias in any patient in whom electrical initiation of the arrhythmia could be achieved only in the presence of antiarrhythmic drugs.

Results of Electrophysiologic-Pharmacologic Testing

Of 262 patients with a history of spontaneous VT studied at our institution, 190 (73%) had inducible VT at the time of initial electrophysiologic evaluation. Multiple logistic regression analysis in this series of patients demonstrates that the most potent predictors of inducibility, in decreasing order of importance, are the presenting arrhythmia, a history of myocardial infarction, and previous number of empiric drug trials (unpublished observations). Of the patients who present with a history of sustained VT, 90% had inducible VT during electrophysiologic studies, compared with 57 and 66% of patients presenting with nonsustained VT and VF, respectively ($p < 0.001$).

For patients with inducible arrhythmias, early studies indicated a high (60 to 70%) success rate in defining an effective antiarrhythmic regimen by serial drug testing.[14,15] More recently, Swerdlow et al[46] defined effective regimens for only 32% of their patients during serial drug testing; this may reflect a more aggressive stimulation protocol than that used in earlier studies.[48] We have used serial drug testing to evaluate 173 patients with spontaneously occurring VT or VF who were found to have inducible arrhythmias at the time of the initial electrophysiologic studies and, thereby, defined therapy that resulted in complete suppression of inducible VT and VF in 118 cases (68%). Stepwise multiple logistic regression analysis was applied to a variety of clinical variables to determine the predictors of a successful response to antiarrhythmic therapy during serial testing. The major determinants of a successful outcome (such as suppression of an inducible arrhythmia) during serial drug testing were, in decreasing order of importance, the number of previous drug trials, the induced arrhythmia (induced sustained VT was harder to suppress than induced nonsustained VT or VF), and the presenting (spontaneous) arrhythmia (unpublished observations). Patients who present with sustained VT

were harder to treat (54% suppression) than those with nonsustained VT (76% suppression) or VF (80% suppression) ($p < 0.001$). This contrasts with the report of Swerdlow et al,[49] who found that the efficacy of acute antiarrhythmic drug trials was predicted by fewer coronary arteries with ≤70% stenosis, female sex, and fewer episodes of arrhythmia. Spielman et al[50] found that by univariate analysis the following 4 factors were associated with successful medical treatment: age <45 years, left ventricular ejection fraction >50%, hypokinesia as the only contraction abnormality and the absence of organic heart disease. Rosen et al[51] examined 41 patients with inducible sustained VT and evaluated the ability of serial drug testing to render VT noninducible or nonsustained ("drug responders"). Logistic regression analysis by these workers demonstrated no independent contribution to outcome by the patient's sex, presence of coronary disease, or cardiomegaly, but the number of empiric drug trials before the electrophysiologic studies was a significant (inversely correlated) independent predictor of outcome. Some, if not all, of these differences may be a result of differences in the stimulation protocols, definitions of a favorable response, antiarrhythmic drugs tested and composition of the patient populations.

Reproducibility of electrophysiologic responses to drugs: The reproducibility of responses to an antiarrhythmic drug during serial electrophysiologic testing is high.[52] We studied 65 patients in whom complete suppression of an inducible arrhythmia (VT or VF) was achieved during serial drug testing. In these 65 patients, repeat programmed ventricular stimulation was performed with precisely the same drug regimen 1 to 5 days later. No attempt was made to control for the time of day at which these studies were performed. Sixty-one of 65 patients (94%) had concordant responses to programmed ventricular stimulation at the time of the second electrophysiologic test with the same antiarrhythmic drug regimen. In 4 patients (6%), discordant responses were observed at the time of the second electrophysiologic test. The presence of inducible VT at the time of the second test in these 4 patients remains unexplained and was not due to significant variations in plasma drug concentrations or a change in the site or mode of ventricular stimulation.

Predictive value of electrophysiologic-pharmacologic testing: Several studies have examined the positive predictive value of electrophysiologic testing in patients with recurrent, life-threatening ventricular tachyarrhythmias. In studies involving several hundred patients, the positive predictive value, defined as the percentage of patients in whom complete arrhythmia suppression is achieved during electrophysiologic testing and in whom no spontaneous arrhythmia occurs at 1 to 2 years of follow-up study, is 90 to 95%.[20,23,39,53,54] The recurrence rate of VT in patients who are discharged from the hospital with a drug regimen on which VT is persistently inducible is 40 to 85% in the series reported to date. Thus, the positive predictive value of electrophysiologic testing (that is, suppression of an inducible arrhythmia predicting a successful outcome) is higher than the negative predictive value (that is, failure to suppress an inducible arrhythmia predicting spontaneous recurrence of the arrhythmia). Swerdlow et al,[53] in a study of 233 patients with sustained VT or VF, showed that in patients with a history of life-threatening ventricular arrhythmias, the 2 most important predictors of freedom from sudden cardiac death are the degree of congestive heart failure as defined by the New York Heart Association classification and the presence of an effective antiarrhythmic drug regimen as defined by electrophysiologic testing. These 2 variables were both powerful and independent predictors of survival in this patient population.[53]

TABLE II Selection of Techniques for Guiding Antiarrhythmic Therapy

Clinical features favoring the use of invasive electrophysiologic techniques:
Recent out-of-hospital cardiac arrest unassociated with acute myocardial infarction
Recurrent episodes of sustained VT with weeks to months between episodes
Infrequent episodes of symptomatic nonsustained VT
Recurrent, unexplained syncope with associated structural heart disease
Clinical features favoring the use of noninvasive monitoring techniques:
Frequently recurring (minutes to hours) sustained VT or VF
Frequently recurring symptomatic nonsustained VT
Exercise-induced VT

VF = ventricular fibrillation; VT = ventricular tachycardia.

Selection of patients for electrophysiologic testing: Electrophysiologic testing is an approach best applied to a specific set of clinical situations. Factors that influence the selection of electrophysiologic versus noninvasive techniques for guiding antiarrhythmic drug therapy are listed in Table II. The role of serial electrophysiologic studies in the treatment of patients with recurrent nonsustained VT is less clear. Empiric therapy using ambulatory electrocardiographic monitoring or exercise stress testing may be more useful when such episodes are frequent. When this is not the case, particularly if the nonsustained VT is rapid, disorganized, and associated with clinical symptoms, serial electrophysiologic studies may be useful in selecting antiarrhythmic therapy insofar as this form of VT may, in some patients, represent a prefibrillatory rhythm associated with a significant risk of sudden death.[55] Although the suppression of induced arrhythmia may afford protection against recurrence in many patients with recurrent nonsustained VT, the precise role of serial electrophysiologic studies in this group of patients is controversial and requires further study.[56,57]

Electrophysiologic evaluation with serial drug testing has also been applied successfully in the management of patients with previous out-of-hospital cardiac arrest. We evaluated electrophysiologic findings in 97 patients who survived an episode of out-of-hospital cardiac arrest unassociated with acute myocardial infarction.[22,39,58] Of the 97 patients, 73 (75%) had inducible VT or VF during programmed cardiac stimulation.

Complete suppression of electrically inducible VT was achieved in 55 of 69 patients who underwent serial antiarrhythmic drug testing or postoperative electrophysiologic evaluation or both; of these 55 patients, 4 (7%) died suddenly during a mean follow-up period of 22 months. Fourteen of the 69 patients still had electrically inducible VT despite pharmacologic, surgical interventions or both; 5 of these patients (36%) had recurrent cardiac arrest or sudden death during the follow-up period. Similar results have been reported by other investigators.[59,60] Thus, programmed cardiac stimulation identifies survivors of prehospital cardiac arrest who require antiarrhythmic therapy and predicts the efficacy of drug regimens and surgery in preventing subsequent recurrence.

Intracardiac electrophysiologic techniques have also been applied to the evaluation of patients with recurrent syncope of unknown origin.[61–64] Suppression of inducible arrhythmias by serial drug evaluation in these patients has been highly predictive of freedom from subsequent recurrent syncope, with a positive predictive accuracy of approximately 85%. However, the sensitivity of electrophysiologic testing techniques in detecting abnormalities in patients with unexplained syncope is far higher in the presence of underlying structural heart disease. Therefore, we recommend electrophysiologic testing in patients with recurrent unexplained syncope only if structural heart disease is present.

Complications of electrophysiologic procedures: DiMarco et al[65] recently reported on the complications associated with programmed cardiac stimulation at this institution. Complications were observed in 20 of 359 patients who underwent programmed electrical stimulation during 1,062 electrophysiologic procedures and included thromboembolism (9 patients), local or systemic infections (6 patients), and pneumothorax (5 patients). The morbidity rate corrected for the total number of separate procedures was 1.9%, and all 20 patients recovered from their complications without long-term sequelae. No procedure-related deaths were observed. On 105 occasions, a sustained ventricular arrhythmia was initiated that could not be interrupted with bursts of rapid ventricular pacing. All 105 of these episodes were terminated successfully by direct-current countershock without need for closed-chest massage or assisted ventilation. Thus, cardiac electrophysiologic procedures are safe when performed by experienced personnel in an appropriately equipped and staffed laboratory. The complications observed during these procedures relate to intravascular catheterization rather than the induction of potentially life-threatening arrhythmias.

Practical Implications

The induction of VT during programmed cardiac stimulation is a highly reproducible, sensitive and specific response in patients with a history of spontaneous sustained ventricular tachyarrhythmias. Furthermore, the complete suppression of inducible VT by an antiarrhythmic drug regimen is highly predictive of freedom from both recurrent arrhythmias and sudden death. As a result, serial electrophysiologic-pharmacologic testing is an extremely useful tool in the selection of antiarrhythmic drug regimens, particularly in patients with life-threatening ventricular tachyarrhythmias.

Many questions remain regarding the use of electrophysiologic techniques in the management of tachycardias. Standardization of nomenclature is lacking. Intracardiac stimulation protocols differ greatly among many laboratories, thereby contributing to substantial variation in the sensitivity and specificity of the technique and making the interpretation and comparison of results difficult. Furthermore, it is unclear whether complete suppression of inducible VT is required to prevent recurrence of spontaneous arrhythmia in all patients or whether "partial" suppression by drugs (for example, a major change in the grade of stimulation required to initiate VT) may be sufficient in some patients. The duration of the predictive value of electrophysiologic testing is yet to be defined. In addition, the management of patients who have no inducible arrhythmias at the time of initial electrophysiologic evaluation remains to be defined. This group constitutes a large subset of patients who present with spontaneous tachyarrhythmias.[30] Finally, prospective comparisons of electrophysiologic techniques with antiarrhythmic therapy directed by ambulatory electrocardiographic monitoring and exercise stress testing in patients with different frequencies and degrees of spontaneous arrhythmias are warranted.

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Definition of Benign Versus Malignant Ventricular Arrhythmias: Targets for Treatment

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The most important characteristics of arrhythmias that determine the need for treatment are the prevalence and clinical significance of the ventricular arrhythmia. Ventricular arrhythmias occur more frequently with advancing age, severity of heart disease and ventricular hypertrophy. Malignant ventricular arrhythmias are of 3 forms: out-of-hospital ventricular fibrillation (VF), recurrent sustained ventricular tachycardia and torsades de pointes ventricular tachycardia in the long QT syndrome. Each condition has a high 1-year mortality rate. Potentially malignant ventricular arrhythmias are ventricular premature complexes (VPCs) of >10 per hour 10 to 16 days after acute infarction and repetitive VPCs. The most malignant arrhythmias occur with severely depressed ventricular function, but VPCs alone have independent prognostic significance. Benign ventricular arrhythmias occur in patients without known heart disease and do not require treatment. The exact effect of frequent and complex VPC in these patients needs further definition. **(Am J Cardiol 1983;52:47C–54C)**

An important and controversial question in antiarrhythmic therapy is: Which ventricular arrhythmias should be treated? Several factors determine decisions about treatment: the mortality force of the ventricular arrhythmias, the presence and perception of symptoms and the efficacy, safety and convenience of treatment. My purpose is to examine the rationale to categorize patients with arrhythmia into groups based on prognosis and to outline which patients should be treated.

A fundamental prerequisite for a rational decision about therapy is knowledge of the prevalence and significance of the ventricular arrhythmias. This knowledge is needed to plan strategies for detection and for treatment. Prevalence of ventricular arrhythmia determines the feasibility of screening programs. The significance of an arrhythmia is an important determinant of treatment. The more malignant a ventricular arrhythmia is, the more important it is to treat it. Benign but symptomatic ventricular arrhythmias also may require treatment to alleviate the annoyance or anxiety they produce.

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For malignant arrhythmias, the primary concern is for efficacy of treatment. Inconvenience and even significant safety risks are worth taking in order to control the most malignant ventricular arrhythmias, such as frequently recurring ventricular fibrillation (VF). For benign arrhythmias, safety is the paramount consideration. Often, the significance of the arrhythmia in terms of short- and long-term morbidity and mortality rates is unknown; this makes decisions about treatment empiric.

Symptoms and patient attitudes often play a critical role in modifying decisions that otherwise would be clear as to the significance of the arrhythmias and the attributes of the best available treatment.

Background Knowledge

Important general facts about ventricular arrhythmias are listed in Table I. Studies using 24-hour electrocardiographic (ECG) recordings show that ventricular arrhythmias are common even in young, normal persons who do not have heart disease.[1–3] The prevalence of ventricular arrhythmias increases with age in subjects without clinically evident heart disease.[4] Also, adjusted for age, the prevalence of ventricular arrhythmias is greater in persons with heart disease.[4] The main feature of heart disease that is associated with ventricular arrhythmias seems to be scarring of the ventricular walls. The broader and more confluent the scarring of the ventricles, the more likely that ventric-

TABLE I Characteristics of Ventricular Arrhythmias in Man

They are common
They increase with age
They increase with ventricular scarring
Infarction
Hypertrophy
Infection
They do not increase with coronary atherosclerosis per se
They can be precipitated/aggravated by exercise
Ischemia
Increased sympathetic activity
Increased heart rate
Electrocardiographically similar arrhythmias may have different causes and significance

ular arrhythmias will occur. There is evidence to suggest that in chronic coronary heart disease, larger scars judged by electrocardiographic Q-wave scores or by left ventricular (LV) ejection fraction (EF) are associated with a significantly greater chance of ventricular arrhythmias.[5–7] The same relation holds early after myocardial infarction.[8] There is strong experimental evidence that infarct size is very strongly related to the inducibility of sustained ventricular tachycardia (VT) with programmed ventricular stimulation and to the VF threshold.[9] The ventricular scarring associated with myocardial hypertrophy in systemic hypertension or valvular heart disease and the fibrosis that follows a variety of diffuse myocardial injuries, for example, viral myocarditis, also increase the likelihood of developing ventricular arrhythmias. The overwhelming importance of scarring in chronic coronary heart disease was shown by Califf et al;[5,6] the extent of coronary atherosclerosis has no significant association with ventricular arrhythmias after adjusting for the association between LVEF and ventricular arrhythmias.

Ventricular arrhythmias may be precipitated or aggravated by exercise.[10] Triggering of arrhythmias by exercise is an important feature to contend with in arrhythmia detection and management. The primary mechanisms of exercise enhancement of arrhythmias are ischemia, enhanced sympathetic activity and the increase in rate per se.

Finally, arrhythmias can appear similar in electrocardiographic recordings but, nevertheless, have different causes and significance. This fact leads to the conclusion that important collateral evidence must be examined before drawing conclusions about how to manage ventricular arrhythmias. I divide the ventricular arrhythmias into malignant, potentially malignant and benign, based on outcome.

Malignant Ventricular Arrhythmias

There are 3 frequently recognized malignant, that is, lethal, ventricular arrhythmias in man: out-of-hospital VF, recurrent sustained VT, and torsades de pointes VT in the long QT syndrome. Each condition has a high mortality rate.

Out-of-hospital cardiac arrest: Much of what we know about the important syndrome of out-of-hospital cardiac arrest comes from work done by community-based emergency medical programs.[11–15] First, coronary heart disease is the most common etiologic form of heart disease in the population that has out-of-hospital cardiac arrest. Cardiomyopathy and valvular heart disease are also well represented. Every series of out-of-hospital cardiac arrest has a small and puzzling group that has no apparent heart disease. Studies by Cobb et al[14,15] show that acute myocardial infarction is not a common cause of out-of-hospital cardiac arrest, especially in patients who are resuscitated and admitted to the hospital. However, significant coronary heart disease is common among the survivors of out-of-hospital cardiac arrest and advanced coronary atherosclerosis, previous myocardial infarction and poor LVEF are all common in this group.[14,15]

Studies to date suggest that the 2 most common causes of out-of-hospital cardiac arrest are ischemic VF and sustained VT that degenerates into VF. Studies by Goldstein et al[16] suggest that as many as half of the out-of-hospital cardiac arrests are caused by ischemic episodes. Many of these episodes result in instantaneous death and the victims are not resuscitated. About 70% of survivors respond to programmed ventricular stimulation with inducible sustained VT that may or may not degenerate into VF.[17–20] This suggests that a similar sequence of events may have occurred during the previous spontaneous cardiac arrest. Kehoe et al[19,20] have presented evidence to support the proposal that some of the noninducible patients had VF as a result of ischemic episodes. Almost all patients who have VT or VF induced during ventricular stimulation have evidence of a ventricular scar, usually from previous myocardial infarction. It is quite likely that studies of survivors of out-of-hospital cardiac arrests are biased, that is, the samples are enriched with scar-related VT or VF. This is because patients with VT are more likely to remain awake, even if symptomatic, during attacks. An extended period of consciousness during VT gives these patients a chance to summon help and to survive until help arrives. Intense myocardial ischemia is more likely to produce abrupt VF without preceding VT and allow the victim no opportunity to seek aid. The longer time from the initiating event to the loss of consciousness in patients with scar-related VT makes it likely that this group is overrepresented among survivors of out-of-hospital cardiac arrest.

Three therapeutic approaches have been proposed for survivors of out-of-hospital cardiac arrest: electrophysiologically guided medical or surgical treatment,[17–20] medical therapy guided by arrhythmias detected during 24-hour ECG recordings and exercise tests[10] and blood level control only.[21] Treatment of survivors of out-of-hospital cardiac arrests is mandatory because untreated patients have a recurrence rate of about 25 to 30% within the year.

Recurrent sustained ventricular tachycardia: Recurrent sustained VT has been the subject of intensive study during the past 5 years. The causes of heart diseases for this arrhythmia are similar to those in survivors of out-of-hospital cardiac arrests. Coronary heart disease and cardiomyopathy account for almost

90% of these patients, with about 75% having coronary heart disease.[22–24] Ventricular scar also plays a major role in the pathogenesis of this syndrome; almost all of the coronary heart disease group have had a previous myocardial infarction and many have had a ventricular aneurysm. Viewed from the perspective of acute myocardial infarction, recurrent sustained VT is a rare syndrome, occurring in the postinfarction year in about 1 to 3 of 1,000 patients. However, these patients accumulate in considerable numbers because myocardial infarction is so common and because these patients often survive multiple episodes of VT. Untreated, recurrent sustained VT has a recurrence or mortality rate of about 40% during a year of follow-up study. Therefore, treatment is imperative. Although there is 1 report of successful treatment of recurrent, sustained VT guided by Holter ECG recordings and exercise testing,[10] the accepted approach to the therapy for this condition is electrophysiologic because the method is sensitive and specific.[25] The recurrence rate is substantially lower for patients who have conversion from inducible to noninducible during electrophysiologic studies done with drug treatment.[26–28] Also, there is substantial success with map-guided arrhythmia surgery in the patients in whom VT remains inducible while receiving the drugs tested.[29] Amiodarone has significant long-term efficacy, although it apparently fails during electrophysiologic studies.[30] There has been no randomized comparison of amiodarone and surgery in patients who have failed with conventional and experimental type 1 antiarrhythmic drugs. Therefore, the better choice between these 2 treatments is not yet clear.

Torsades de pointes in the long QT syndrome: Torsades de pointes is a rapid polymorphic VT with unique ECG features: The polarity of the QRS complex repeatedly twists from upright to inverted and back.[31] This type of ECG appearance usually is associated with a prolonged QT interval. There are 2 congenital forms of the long QT syndrome: one has dominant inheritance and is associated with congenital deafness and one has recessive inheritance and has no association with deafness.[32] In addition, there is a so-called acquired form of the long QT syndrome that is usually caused by electrolyte abnormalities, such as hypokalemia or hypomagnesemia or drug toxicity (for example, quinidine or tricyclic antidepressants).[33] As suggested by its bizarre ECG appearance, torsades de pointes is an unstable form of VT and is likely to deteriorate into VF.

There is no doubt that torsades de pointes is a malignant arrhythmia that requires treatment. The approach to therapy of this condition is as unusual as the ECG appearance. Emergency treatment includes *avoidance* of type I antiarrhythmic drugs, use of ventricular pacing and, occasionally, infusion of catecholamines. Evaluation of therapy usually is accomplished by on-line, real-time ECG monitoring and later by 24-hour ECG recordings. Long-term drug treatment almost always includes beta-adrenergic blocking agents and occasionally phenytoin. Drug-resistant cases usually can be successfully treated by left stellate ganglionectomy.[33–35]

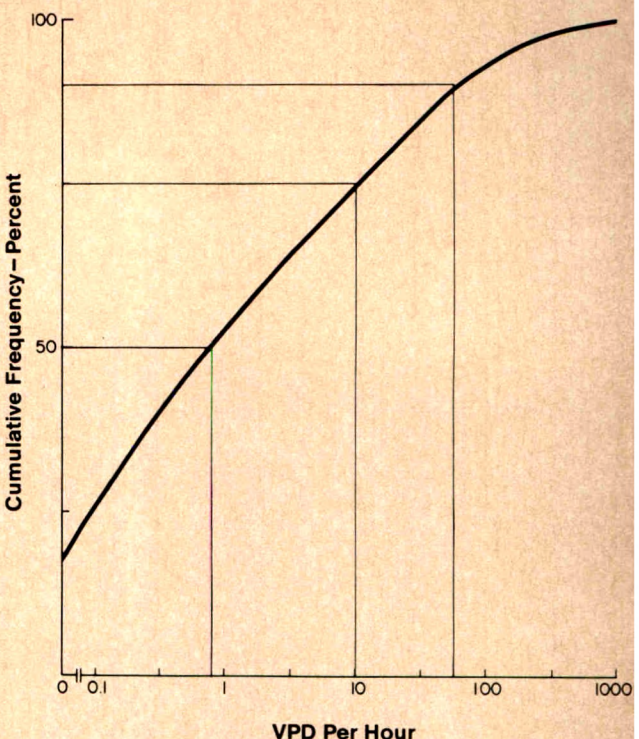

FIGURE 1. Cumulative frequency distribution of ventricular premature complexes (or depolarizations [VPDs]) expressed as the hourly average over 24-hours. The 50th percentile is just below 1 VPD/hour, the 75th percentile is at 10 VPDs/hour and the 90th percentile is at 60 VPDs/hour.

Potentially Malignant Ventricular Arrhythmias

The aforementioned arrhythmias classified as "malignant" were all examples of sustained ventricular activity. Studies performed over the past 10 years have identified several "potentially malignant" ventricular arrhythmias. These include frequent and repetitive but nonsustained ventricular premature complexes (VPCs) in patients with coronary heart disease, particularly those with previous myocardial infarction, and in patients with cardiomyopathy. Because the significance of ventricular arrhythmias in coronary heart disease and cardiomyopathy appears to be similar, these will be discussed together.

Frequent ventricular premature complexes: The prevalence and significance of ventricular arrhythmias in coronary heart disease have usually been studied after acute myocardial infarction. Most studies were done at about the time of patient discharge after an index myocardial infarction because this is a convenient time for both physician and patient and because of the high mortality rate 6 to 12 months after infarction.[36–39] The prevalence of VPCs 10 to 16 days after myocardial infarction is shown in Figure 1. Fifteen to 20% have no VPCs in a 24-hour recording, about 50% have an average of <1 per hour, 20 to 25% have ≥ 10 per hour, and only 5% have ≥ 100 per hour. The time between myocardial infarction and the 24-hour recording is an important determinant of VPC prevalence. If 24-hour recordings

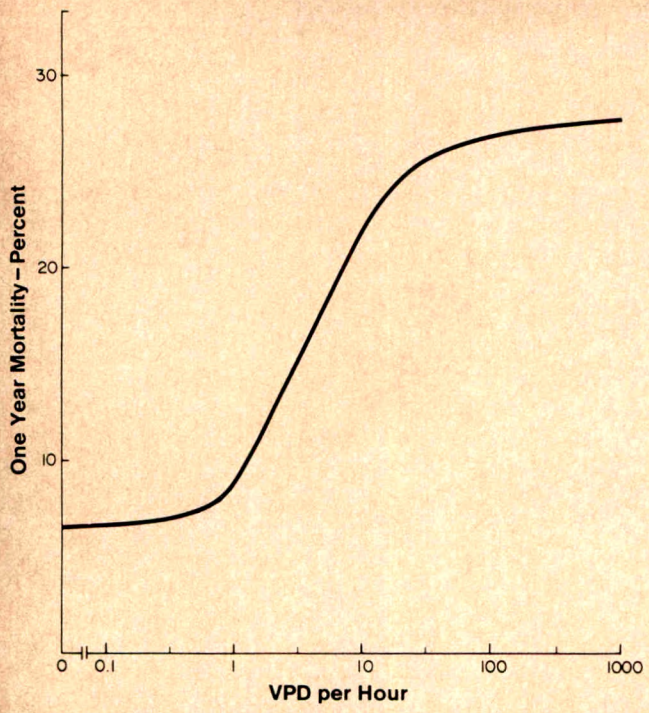

FIGURE 2. Mortality rate as a function of average hourly frequency of ventricular premature complexes (or depolarizations [VPDs]). Patients with <1 VPD/hour have a low mortality rate. The mortality rate increases sharply as a function of VPC frequency and reaches a plateau from 10 to 30 VPDs/hour.

are made at 3 to 5 days after infarction, any level of VPC frequency is less prevalent. Recordings made 6 to 12 weeks after infarction show a higher prevalence of frequent VPCs. The relation between the first-year postdischarge mortality rate and frequency of VPCs is shown in Figure 2. Interestingly, the relation is S-shaped. About half of the VPC-associated mortality rate increase is achieved at frequencies of 1 per hour and the mortality rate plateaus are at about 10 per hour. This means that the mortality rate is 20 to 25% for patients with ≥10 VPCs; patients with ≥100 per hour are at no greater risk than those with 10 to 100 per hour. As mentioned by Furberg elsewhere in this symposium, there has been no definitive trial to evaluate whether reducing the frequency of VPCs has a beneficial influence on postinfarction mortality rates. If one assumes that treatment can reduce mortality, one would reasonably conclude that patients with VPC frequencies >10 per hour should be treated; a cogent argument can be made for using an even lower frequency value as the criterion for treatment. The relation in Figure 2 calls into question the conventional frequency criteria for treatment of ventricular arrhythmias after infarction, usually 60 to 100 per hour or even more.

TABLE II Relation Between Repetitive Ventricular Premature Complexes and Mortality, Adjusted for the Effects of Frequency of Ventricular Premature Complexes

VPC Frequency (per hour)	Repetitive VPCs	Status		Total	Mortality	Odds Ratio
		Dead	Alive			
<10	Absent	31	349	380	8%	. . .
	Present	16	68	84	19%	2.7
≥10	Absent	6	36	42	14%	. . .
	Present	31	79	110	28%	2.2
	Total	84	532	616	14%	. . .

Chi-square total = 12.11, df = 2; chi-square interaction = 0.59, df = 1; chi-square association = 11.52, df = 1; summary odds ratio = 2.5.
VPC = ventricular premature complex.

Repetitive ventricular premature complexes: The complex feature of postinfarction VPC with the greatest significance is repetitiveness. Multiform VPCs have very little significance and R-on-T complexes have less prognostic significance.[38,39] About 25% of 24-hour predischarge ECG recordings contain repetitive VPCs; about 15% contain paired complexes only, and 10% contain both paired complexes and ≥1 episodes of nonsustained VPC runs (≥3 consecutive ventricular complexes at any rate). Recordings with runs but no pairs are extremely rare, only about 5% of the recordings with runs. The significance of repetitive VPCs in a Columbia University study is shown in Table II, adjusted for VPC frequency. Overall, the odds of dying are 2.5 times greater for patients who have repetitive VPCs compared with those who do not. Although there is a significant and moderately strong association between VPC frequency and repetitive VPCs, there is no interaction between these 2 factors with respect to mortality. The mortality rate for patients with VPC runs is sig-

TABLE III Ventricular Tachycardia Recorded Just Before Discharge From Hospital After Myocardial Infarction

Study	No. of Patients	Age Limit (yr)	1-Year Mortality	Duration of Recording (hours)	Ventricular Tachycardia	
					Definition of VT	No. With VT (%)
Anderson et al[40]	915	<66	4%	6	≥3 VPC >100/min	10 (1.1)
Bigger et al[41]	430	<76	13%	24	≥3 VPC Any rate	50 (11.6)
Kleiger et al[42]	289	<71	9%	10	≥3 VPC Any rate	10 (3.4)

VPC = ventricular premature complex. VT = ventricular tachycardia.

TABLE IV Nonsustained Ventricular Tachycardia After Infarction and Long-Term Mortality

Study	Patients (n)	Age	Follow-up (months)	Mortality (%) With VT	Mortality (%) Without VT
Anderson et al[40]	915	<66	48	25	13
Bigger et al[41]	430	<76	36	38	19
Kleiger et al[41]	289	<71	12	14	7

VT = ventricular tachycardia.

nificantly higher than for patients with pairs but no runs (chi-square association 11.52; $p < 0.001$). Adjusting for VPC frequency dichotomized at 10 per hour with the Mantel-Haenszel chi-square procedure or with logistic regression models, we found that repetitive VPCs add significantly and independently to the risk of dying. Table III is a summary of the 3 major studies of nonsustained VT in patients with recent myocardial infarction.[40–42] The prevalence of VT at the time of hospital discharge varies with age and base mortality rate, the recording duration, the sensitivity of the analysis method, and the definition of VT. If predischarge 24-hour recordings are done in a representative cross-sectional sample of the U.S. postinfarction population with a 10% 1-year mortality rate and then are analyzed by sensitive digital computer methods, the prevalence of VT is about 10%. The mortality influence of VT is large and remarkably constant across the 3 major studies (Table IV). In patients with runs, no relation has been found between the number of episodes of runs or the length of the runs and mortality in a year or more of follow-up (Fig. 3). However, the studies to date have been small and have not had much power to detect such relations should they exist. Nearly all episodes of VPC runs recorded predischarge are brief, infrequent, and asymptomatic.[40,41] Half of the patients have only 3 VPCs in the longest run and 30% have only a single run in the 24-hour recording. Considering these facts, it is remarkable that patients with runs have such a high mortality rate during follow-up study after infarction.

Relation of ventricular arrhythmias to left ventricular dysfunction: There are 2 hypotheses about the relation between ventricular arrhythmias and LV dysfunction: that ventricular arrhythmias contribute independent mortality force after adjusting for LV dysfunction, and that ventricular arrhythmias are strongly associated with LV dysfunction and that ventricular arrhythmias do not contribute independently to mortality after adjusting for LV dysfunction. Ruberman,[39] Moss,[37] and their co-workers analyzed for a relation between "complex" ventricular arrhythmias (bigeminy, multiform, pairs, runs or R on T) and postinfarction mortality rates, adjusting for LV dysfunction using the clinical diagnosis of heart failure. Both of these studies were large—1,739 and 940 patients, respectively; both used fairly brief ECG recordings, 1 hour and 6 hours, respectively; and both used clinical heart failure to adjust for LV dysfunction. Both analyses yielded a similar result: complex ventricular arrhythmias were significantly associated with follow-up mortality after adjusting for LV dysfunction. In a study of 395 coronary heart disease patients referred for cardiac catheterization, Califf et al[6] addressed the same question; only 53% of their patients had a previous myocardial infarction and most of these were in the remote past. Angiographic LVEF was used to adjust for LV dysfunction. A hierarchical scoring system using frequency, multiformity,

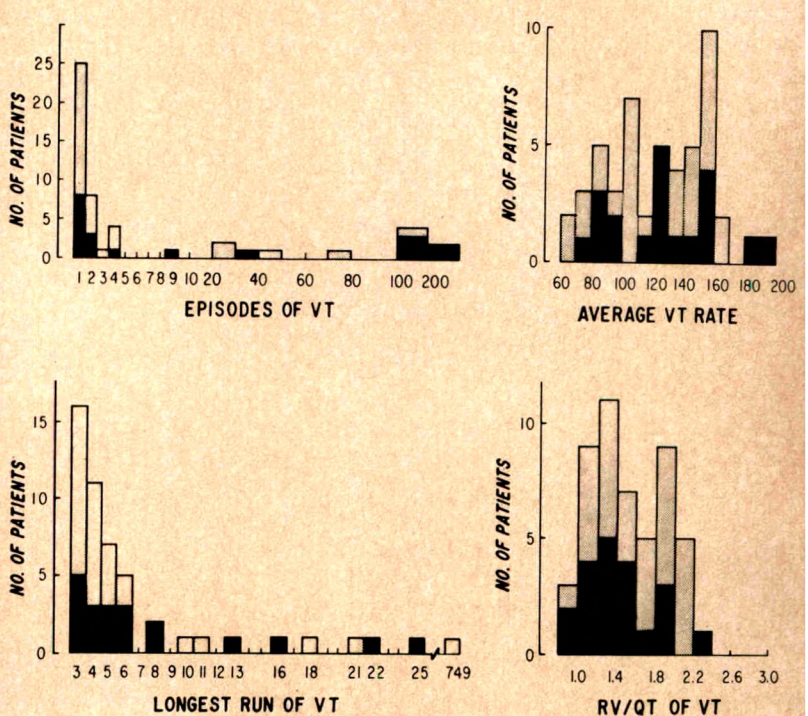

FIGURE 3. Characteristics of ventricular tachycardia (VT) 2 weeks after myocardial infarction in 50 patients. The **black portion** of the **bars** indicates the deaths. There is no indication that patients with more frequent, longer or faster episodes of VT have a higher death rate. However, this sample is too small to settle this question definitively. Reproduced from Bigger et al[41] with permission of the publisher.

TABLE V Mortality 1 Year After Infarction as a Function of Left Ventricular Ejection Fraction and Repetitive Ventricular Premature Complexes[43]

Ejection Fraction (%)	Repetitive VPCs	Status				Odds Ratio
		Dead	Alive	Total	Mortality	
>40	Absent	3	196	199	2%	...
	Present	4	51	55	7%	4.9
≤40	Absent	6	81	87	7%	...
	Present	12	35	47	25%	4.4
	Total	25	363	388	6%	...

Chi-square total = 14.37, df = 2; chi-square interaction = 0.27, df = 1; chi-square association = 14.10, df = 1; summary odds ratio = 4.8.
VPCs = ventricular premature complexes.

TABLE VI One-Year Mortality Rate in Patients With Inducible Ventricular Tachycardia/Ventricular Fibrillation After Myocardial Infarction[46]

Inducible VT/VF	Death in 1 Year		
	Present	Absent	Total
Present	10	28	38
Absent	7	120	127
Total	17	148	165

Mortality with VT/VF: 26%, mortality without VT/VF: 6%.
$p < 0.01$, odds ratio = 5.9.
VF = ventricular fibrillation; VT = ventricular tachycardia.

pairs and runs was used to grade the arrhythmias detected using a conventional Holter scanner to analyze 24-hour ECG recordings. However, after adjusting for LVEF, there was no significant independent relation between ventricular arrhythmias and mortality. However, when Califf et al used only clinical and noninvasive measures to adjust for LV dysfunction, they obtained a result similar to that of Ruberman and Moss. This analysis failed to eradicate the relation between ventricular arrhythmias and mortality. Thus, they concluded that the adjustment procedure of Ruberman and Moss failed because they used inadequate variables to represent LV dysfunction. Although the findings of Califf et al[6] were not obtained in patients with recent myocardial infarction, they nevertheless seriously challenge the conclusions of Ruberman[39] and Moss.[37] More recently, 2 studies have used radionuclide EF to adjust for LV dysfunction in postinfarction patients. The Multicenter Investigation of the Limitation of Infarct Size (MILIS)[43] reported findings in 388 patients (Table V) and the Multicenter Post Infarction Program (MPIP)[44] in 766 patients. Both of these studies used sensitive and specific computerized methods to analyze the 24-hour electrocardiograms and radionuclide methods to measure LVEF. In these preliminary analyses, MILIS used repetitive VPCs and MPIP used VPC frequency dichotomized at 10 per hour as arrhythmia endpoints. Both studies show that ventricular arrhythmias do contribute *independently* to the mortality risk in the year after myocardial infarction. This was an important point to settle because it forms a critical basis for treatment strategies aimed at reducing postinfarction death.

Our own working hypothesis is that ventricular arrhythmias are significantly and independently related to subsequent cardiac death in patients with coronary heart disease or cardiomyopathy. Also, we believe that certain patients with coronary heart disease and large scars have ventricles capable of supporting reentrant activity and VF even though these patients may not have significant ventricular arrhythmias in 24-hour ECG recordings. The subgroup with arrhythmogenic scars may be detected by programmed ventricular stimulation. Already there is some preliminary evidence for this hypothesis. Hamer,[45] Richards,[46] and their coworkers found that patients with recent myocardial infarction who have VT or VF in response to programmed ventricular stimulation have a 5- to 6-fold increased likelihood of having death or symptomatic arrhythmias in follow-up (Table VI). Hamer et al did a preliminary and superficial comparison of electrophysiologic studies and Holter recordings before the patients were discharged after myocardial infarction and found a rather poor correlation. So far, preliminary studies show very encouraging results, indicating that from among the group with large, confluent myocardial scars caused by infarction, programmed ventricular stimulation can be used to identify those who have the greatest potential for arrhythmic death. The relation between positive response to programmed ventricular stimulation early after myocardial infarction and spontaneous ventricular arrhythmias is not yet defined.

Benign Ventricular Arrhythmias

A number of studies have been done in apparently normal patients to determine the prevalence of ventricular arrhythmias and their significance. In a small study of 50 male medical students, Brodsky et al[1] found that 25 (50%) had some ventricular arrhythmia, but only 2% had >50 VPCs per 24 hours and only 4% had repetitive VPCs. Frequent and repetitive VPCs were found more often in Hinkle et al's[47] study of 301 apparently normal middle-aged men (median age 55 years) in a random population sample. To eliminate persons with asymptomatic coronary heart disease in their sample, Kostis et al[48] selected for study a group of 101 persons from 1,500 patients who were referred for coronary angiography. These 101 patients were normal as judged by physical examination, electrocardiography, chest roentgenography, echocardiography, exercise test, coronary angiography, and left ventriculography.[48] The group had a mean age of 49 years (range 16 to 68). The prevalence of VPC frequency was as follows: >1 per hour, 39%; >10 per hour, 20%; and >100 per hour, 4%. No repetitive forms were detected in any of the 101 patients and other complex forms were rare as well; multiform VPCs were found in only 4% and R and T in 2%. These findings are strikingly different from those of previous studies. The prevalence of VPC frequency in the Kostis sample is very similar to that found in patients with recent myocardial infarction. However,

the almost total lack of repetitive VPCs is the striking aspect of the study. This finding is in marked contrast to the findings in patients with heart disease[4] or in middle-aged men.[47] If validated, those findings indicate that the striking difference between normal and abnormal middle-aged persons is the prevalence of repetitive VPCs. Kennedy et al[49] asked the opposite question: whether or not frequent and complex ventricular ectopic activity indicates underlying coronary heart disease. From a group of 62 patients with ≥100 VPCs per hour and repetitive VPCs but normal 12-lead electrocardiogram, M-mode echocardiogram, and exercise test results, 25 were selected for coronary angiography. The primary indication for angiography was the presence of ventricular arrhythmias in association with coronary risk factors. The average age in the group was 47 years and the ventricular arrhythmias had been present for an average of 3 years. Coronary angiography showed significant coronary lesions in 25% (6 of 25) of the group. This study is very small and should be extended, but tends to support the view that most patients who have striking ventricular arrhythmias but normal noninvasive workup results do not have significant coronary heart disease.

Follow-up studies show that normal subjects who have frequent ventricular arrhythmias have an excellent life expectancy without antiarrhythmic drug treatment for follow-up periods of about 2 years. With the studies done so far, it is not possible to say that ventricular arrhythmias do not increase the risk of dying in normal persons compared with appropriate control groups. Given the mortality expectations for normal persons and assuming the same increment in risk attributable to VPCs as occurs in postinfarction populations (that is, relative risks of 2.0 to 3.0), a very large study would be required to detect such a difference. The sample size required would have to be well above 1,000 subjects. Nevertheless, one can say that the mortality rate in persons with apparently normal hearts and frequent ventricular arrhythmias is reasonably good. Given our current antiarrhythmic drugs, it is well not to treat these patients unless they are symptomatic or the arrhythmia demonstrates clear-cut malignant potential.

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Treatment and Prophylaxis of Ventricular Arrhythmias in Acute Myocardial Infarction

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Remarkable advances have been made in the management of cardiac disease in the last 20 years, but antiarrhythmic drug strategy in the acute phase of myocardial infarction remains less than satisfactory. Primary ventricular fibrillation (VF), once considered predictable on the basis of detection of "warning arrhythmias," cannot be anticipated. Management must be either expectant or prophylactic. Restriction of drug use to selected patients and the apparent lack of effect of VF on late prognosis argue for the former approach, yet safe and effective prevention of VF is an attractive therapeutic goal. High-dose intravenous lidocaine probably offers efficacy but the risk-benefit ratio of this regimen is still debated. Adoption of a prophylactic regimen mandates drug administration to a large number of patients who either are not at risk of developing VF (noninfarct patients) or who are destined not to develop VF (70 to 95% of infarct patients). Ventricular arrhythmias other than VF are common in acute infarction and, for emotional rather than scientific reasons, often are aggressively treated. Little evidence exists to support this management. Few ventricular arrhythmias at this time in infarction have either immediate importance or prognostic significance. Reevaluation of antiarrhythmic drug use and arrhythmia treatment in acute myocardial infarction is long overdue. However, there is a paucity of controlled data upon which to base new strategies, and clinical research in this field is hampered by ethical considerations, by rigidly held but unscientifically based beliefs and by a lack of fundamental knowledge of arrhythmia mechanisms and their significance.

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Acute myocardial infarction (MI) is a dramatic clinical event associated with a high initial mortality rate. Ventricular fibrillation (VF) was identified as the major cause of death over 20 years ago but the association of ventricular arrhythmias and MI has been recognized for much longer. In 1586, Diversus provided a clear description when he wrote, "two signs indicate impending cardiac syncope and sudden death; first a sensation of sudden constriction of the heart . . . and second . . . an intermittent pulse." Since the establishment of coronary care units and the widespread availability of defibrillators, the emphasis of arrhythmia management has changed from the treatment of VF to the prediction and prevention of this arrhythmia. Yet, as more is understood of the natural history of MI and of the action of antiarrhythmic drugs, the optimal management of arrhythmias in early MI remains unclear.

The various strategies for antiarrhythmic drug administration that have been advocated and applied include selective use in patients with "warning arrhythmias," unselective prophylactic use in all patients with suspected acute MI, and use only in the treatment of VF and hemodynamically significant arrhythmias. In the United States, prophylactic lidocaine therapy is given to the majority of patients with suspected acute MI in an effort to prevent primary VF.

In Europe, where this policy is less common, greater reliance has been placed on speedy management of VF when it occurs or on selective prophylactic drug administration. No well-conducted comparisons of these various regimens have been made, largely because of the complexity of such an investigation and because of the large number of patients required. Moreover, VF occurring in hospital is rarely fatal, and it is unlikely that there is an important difference in hospital mortality rates related to methods of antiarrhythmic drug use. Less certain is whether the long-term mortality rate is influenced by short-term arrhythmia management.

Frequency of ventricular arrhythmias in acute myocardial infarction: After the onset of symptoms of MI, the incidence of primary VF decreases exponentially with time and becomes rare after 12 hours.[1,2] This marked time dependency hampers definition of

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TABLE I Categories of Ventricular Fibrillation

Myocardial ischemia
VF ("primary")—high recurrence rate
Myocardial infarction
Primary VF—no shock or failure
Rx 95% success, recurrence rare, prognosis good
Secondary VF—shock or failure or both
Rx 30% success, recurrence common, prognosis bad
Iatrogenic VF—e.g., catheter, drugs
Recurrence rare (if cause recognized), prognosis good
Late VF—48 hours after acute event
Rx? success? recurrence common, prognosis bad

Rx = therapy; VF = ventricular fibrillation.

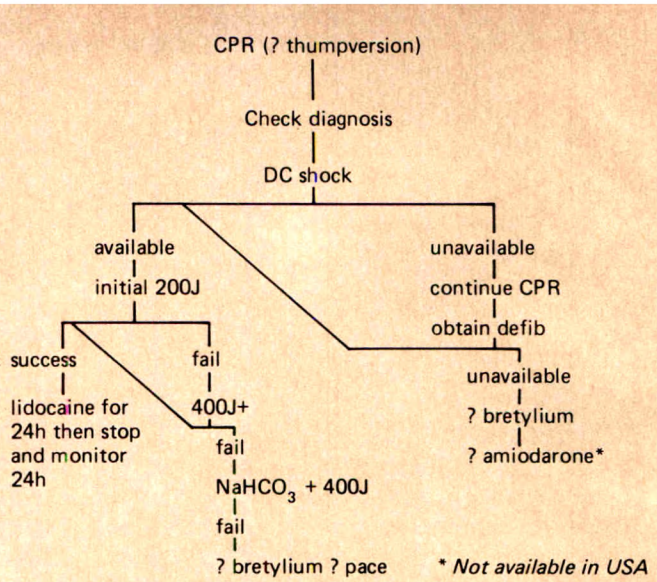

FIGURE 1. Suggested management for ventricular fibrillation. CPR = cardiopulmonary resuscitation; DC = direct-current.

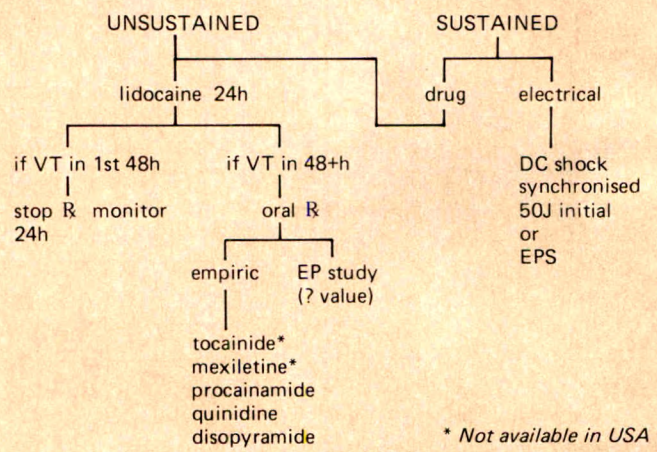

FIGURE 2. Suggested management for ventricular tachycardia (VT). DC = direct-current; EP and EPS = electrophysiologic study.

VF frequency, but current estimates suggest a rate of ≤30% in the first hour. The observed incidence of VF in the coronary care unit depends upon the patient population's time from onset of symptoms to admission. VF rates during transit to hospital are similarly time-dependent, but are also related to the duration of observation.

Early reports from coronary care units suggested that in approximately 10% of patients VF would develop.[3,4] However, in recent studies,[5,6] the VF rate in the coronary care unit has been closer to 5% in patients not given antiarrhythmic therapy. Whether this difference represents a true decrease in incidence or reflects a change in arrhythmia analysis is unclear. Various categories of VF are now recognized and include VF in the setting of myocardial ischemia, primary VF, secondary VF, iatrogenic VF and late VF. Resuscitation success rate and prognosis for each type is different (Table I). Some reports of coronary care unit experience do not separate these categories, whereas others detail only primary VF.

It has been widely believed that the incidence of all arrhythmias decreases exponentially from the onset of symptoms, but very little information has been derived from continously recorded electrocardiograms. VF is rarely missed in the coronary care unit, but recognition of other ventricular arrhythmias by observation or by alarm systems is not so reliable.

A recent study[2] investigated the natural history of ventricular arrhythmias in acute MI. Arrhythmia analysis was from continuously recorded electrocardiographic tapes. During the investigation, patients received no antiarrhythmic therapy other than for hemodynamically important arrhythmias. Patients enrolled in this investigation had not received beta-adrenoreceptor blocking drugs, diuretics, or digoxin either before inclusion or subsequent to their MI. In the first 4 hours after the onset of symptoms, all types of ventricular arrhythmias were relatively frequent but after 4 hours, primary VF and R-on-T ventricular ectopic complex frequency decreased rapidly and the incidence of other ventricular arrhythmias (ventricular tachycardia [VT], ventricular ectopic pairs and isolated ventricular ectopic complexes) appeared to increase. This bimodal distribution of arrhythmias comprises an early phase characterized by a high incidence of VF and R-on-T ventricular ectopic complexes that may reflect a reentrant mechanism. In the late phase, other ventricular arrhythmias predominate and possibly reflect a different pathophysiologic arrhythmia mechanism.

In patients with MI who have not received antiarrhythmic therapy, VT (≥3 consecutive ventricular ectopic complexes at a rate ≥120/min) is a relatively common arrhythmia, detected in ≤73% of patients within the first 24 hours of symptoms.[5,6] Longer runs of consecutive ventricular ectopic complex beats (≥10 consecutive complexes at a rate ≥120/min) occur in up to 27% of patients.[5,6] However, sustained VT is relatively uncommon at this time. Other ventricular arrhythmias (ventricular ectopic complex pairs and isolated ventricular ectopic complexes) are also common and are detected in almost 100% of patients during the first 24 hours of their illness.

TABLE II Relation of Warning Arrhythmias to Ventricular Fibrillation

	Frequency of WA	
	Total Group	VF patients
Lie et al[15]	59%	60%
El-Sherif et al[16]	55%	58%

Warning arrhythmias (ventricular ectopic complexes >5/minute, multiform, repetitive, R-on-T).
VF = ventricular fibrillation; WA = warning arrhythmias.

TABLE III Comparative Accuracy of Computer and Human Arrhythmia Detection. Ventricular Arrhythmia Detection—Conventional Versus Computer

		Accuracy (%)	
	Actual Incidence (%)	Conventional System	Computer
VF	5	100	100
R-on-T VECs	55	12	40
VT	28	11	88
VECs	90–100	66	95

VECs = ventricular ectopic complexes; VF = ventricular fibrillation; VT = ventricular tachycardia.
Figures are calculated for illustrative purposes.[1,2,3,17,18]

Importance of ventricular arrhythmias in acute myocardial infarction: Ventricular arrhythmias are important if they cause symptoms, are hemodynamically significant or have prognostic significance.

Unless rapidly treated, primary VF is fatal, although a small proportion of episodes do spontaneously terminate.[7] Management includes prompt application of a direct-current shock and should incorporate prophylactic therapy for 24 hours, because the electrophysiologic milieu that supported the initial event is unaltered by the direct-current shock and is likely to remain until the infarction process has undergone sequential change. Recurrence after 24 hours is unlikely. Figure 1 shows a suggested management plan for VF. Primary VF complicating acute MI appears to confer little or no late adverse prognostic significance.[8–10] One-, 5- and 10-year survival rates for resuscitated patients are excellent and are not different from those for patients whose infarction was not so complicated.

The lack of a generally agreed upon definition for VT confounds analysis of the importance of this arrhythmia. One study noted that VT occurring in the acute coronary care unit phase of infarction conferred no late adverse prognostic significance.[11] The immediate impact of VT depends upon its rate and duration. In acute MI, there appears to be no relation between VT and VF[2] and the decision to treat VT must depend upon clinical circumstances and physician preference. The treatment of rapid VT may be modified depending on whether the arrhythmia is sustained or paroxysmal. A suggested management strategy is shown in Figure 2.

Warning arrhythmias: A variety of ventricular arrhythmias have been suggested to be harbingers of primary VF[12] and are graded by the Lown classification.[13] Their predictive role was based on oscilloscopic observations of patients' electrocardiograms in the early phase of acute MI. Soon after establishment of coronary care units, much effort was put into detecting these so-called warning arrhythmias and suppressing them with lidocaine. Doubts regarding the value of this therapy were voiced[14] but it was not until the studies of Lie,[15] El-Sherif,[16] and their co-workers, using continuous electrocardiographic recording and analysis, that an accurate assessment of the relevance of warning arrhythmias was possible. Both studies showed that warning arrhythmias (defined as ventricular ectopic complexes with a frequency >5/minute, multiform ventricular ectopic complexs, VT, and R-on-T ventricular ectopic complexes) were as common in all infarct patients as they were in the subgroup who progressed to VF (Table II). This finding, which contradicted previous observations, can be explained by the inaccuracy of human observations of electrocardiographic displays (Table III).[17,18] However, human detection of an arrhythmia probably becomes more reliable with increasing or changing prevalence of the event. A change of frequency of R-on-T ventricular ectopic complexes has been reported before the onset of primary VF in selected infarct patients.[2] This change of frequency may be the phenomenon that aided recognition of R-on-T ventricular ectopic complexes by observers and became the basis for their categorization as the most "malignant" arrhythmia in the Lown classification. However, despite the association between a change of R-on-T prevalence and primary VF, the phenomenon appears insufficiently sensitive to operate as a practical predictor of VF.[2] No electrocardiographic event yet identified can predict satisfactorily the occurrence of VF. The role of monitoring in the coronary care unit must then be questioned because its rationale in detecting warning arrhythmias no longer has clinical purpose. However, substantial resources continue to be expended in equipping and staffing coronary care units to perform this task. This is not to deny the possible benefits of electrocardiographic monitoring, but if the relevance of arrhythmias were better understood, more appropriate monitoring systems might be developed. Current monitoring facilities that offer moderately reliable ventricular arrhythmia detection by real-time computers are valuable research tools but offer little in the clinical management of patients.

Prophylaxis of ventricular arrhythmias in acute myocardial infarction: The standard policy in some cardiac centers is to give no antiarrhythmic therapy except for the treatment of hemodynamically significant or symptomatic arrhythmias. VF, when it occurs, is promptly and aggressively treated. In other centers, unease regarding VF has stimulated the search for safe prophylactic remedies that could be administered to unselected populations of patients with suspected acute MI.

Many studies of prophylactic antiarrhythmic therapy in acute MI have been reported,[19] but few have provided definite conclusions regarding efficacy. Often, too few

TABLE IV Studies of Ventricular Arrhythmia Prophylaxis With Lidocaine

	N	Dose	VF Incidence (%) Untreated	Treated
Bennett et al[21]	256	Low	5.6	3.8
Mogensen et al[22]	77	Mod	2.7	0
Church and Biern[23]	86	Mod	6.8	9.5
Bleifield et al[25]	89	Mod	4.2	0
O'Brien et al[26]	300	Mod	3.4	4.5
Lie et al[20]	212	High	10.5	0

Mod = moderate; VF = ventricular fibrillation.
Adapted from De Silva et al.[27]

episodes of VF have occurred for a direct evaluation of drug effect. Inferred benefit from drug effect on VT, although often made, is no longer tenable[2] because this arrhythmia behaves differently and may have disparate pathophysiologic mechanisms. A statistically significant reduction of primary VF has been shown in only 1 controlled study. In this investigation, high-dose intravenous lidocaine was used.[20] The incidence of primary VF in the control group was 9%. No VF occurred in the lidocaine-treated group. These figures permitted identification of drug effect in a surprisingly small number of randomized patients. Other studies of lidocaine[21–25] have failed to show this benefit but none were of similar design[26] (Table IV). Uncontrolled but impressive data on prophylactic lidocaine have been reported by Wyman and Hammersmith.[27] Despite the paucity of evidence, it is likely that high-dose intravenous lidocaine prevents primary VF, but Lie et al[20] reported that the recommended regimen produced unwanted effects in 15% of patients. Most were minor. In an earlier, lower-dose study,[22] serious consequences of prophylactic lidocaine were observed in patients suspected of acute MI but in whom the diagnosis was not confirmed by sequential electrocardiographic and enzymatic analysis. In the study of Lie et al,[20] the consequences of drug administration to noninfarct patients was not reported.

Arrhythmogenesis is a topical issue. It has been suggested that subtherapeutic plasma levels of lidocaine in early acute MI might predispose to arrhythmia development. This important possibility has not been examined scientifically in clinical practice.

VF prophylaxis with other antiarrhythmic drugs has been investigated.[19,28] Many early studies were designed and conducted when the time-dependent nature of VF was unappreciated. Initially promising results with prophylactic disopyramide[29,30] have not been confirmed in later studies.[31,32] Prophylactic tocainide[6] and mexiletine[5] have proved highly effective in reducing VT, but assessment of the effect of these drugs on VF was precluded by low VF rates in the selected populations. The most important general conclusion to be drawn from these reports is that prophylactic oral antiarrhythmic therapy has little chance of preventing primary VF. Gastrointestinal absorption of most orally administered drugs is reduced by acute MI and by the administration of narcotic analgesic,[33] and it is unlikely that any could achieve "therapeutic" plasma concentrations within 1 hour of dosing. A delay of this magnitude is critical in the early phase of acute MI.

Successful prophylactic regimens require parental administration. The intravenous route is the fastest method of achieving satisfactory plasma levels, but may be the dosing method most likely to produce unwanted effects. Moreover, initiation of intravenous therapy requires skilled medical or paramedical attendance, precluding use of this route by the lay population or even by patients themselves.

Other approaches to ventricular arrhythmia control: Important factors responsible for arrhythmias in acute MI include ischemia, catecholamine release and electrolyte shifts. Dispersion of refractoriness is created and predisposes to the development of reentrant arrhythmias such as VF and R-on-T ventricular ectopic complexes. The pathway by which the basic disturbances produce the electrophysiologic changes is not well understood and metabolic interventions that have a good theoretical basis are not applicable to clinical management.[34]

Beta-adrenoreceptor blocking drugs that have an important role in the prophylaxis of sudden death after recovery from infarction may be useful in the acute stage. Most studies have been started too late to investigate this possibility, but in 1 study of metoprolol,[35] early benefit was claimed. Further investigation of the efficacy and safety of beta-adrenoreceptor blocking drugs in the first 24 hours of infarction is indicated.

Conclusions

Ventricular arrhythmias are a common complication of acute MI. The observed incidence of VF varies with time from the onset of symptoms, with a rate of >30% in the community and 4 to 10% in hospital coronary care unit populations. VF cannot be predicted, but the likelihood of the event is highest in the first few minutes after the onset of symptoms. VT is a common arrhythmia in acute MI and has a time course that differs from that of primary VF. Depending on its definition, it is present in <70% of patients but is only rarely symptomatic or of hemodynamic significance at this time and, if nonsustained, appears to have no late prognostic significance.

From these variables, a management strategy for ventricular arrhythmias in acute MI can be formulated. Therapy based on warning arrhythmias has no scientific foundation. The management of VF must be either expectant or prophylactic. Expectant management is safe, restricted only to those at risk and has an excellent immediate and long-term success rate. Well-trained staff and reliable and instantly available equipment are mandatory. Proved prophylactic therapy means using a high-dose lidocaine regimen. Although probably effective, the risk-benefit ratio of this strategy is still undefined.[36,37] The drug must be administered to patients who later are shown not to have sustained an infarct and who are not at risk of VF. They may constitute as much as 50% of coronary care unit admissions. Care

must be taken to avoid lidocaine overdosing, but in general the management demands less of the attending staff and may be particularly appropriate for patients who must be cared for in less-than-ideal cardiologic circumstances.

Except for VF, most acute phase ventricular arrhythmias probably do not require therapy, but those causing upsetting symptoms or those with hemodynamic importance should be treated. The required duration of therapy is difficult to define. An event in the first 24 hours may well be self-limiting and not recur after initial therapy. Events that do recur or that are considered to be likely to recur require oral therapy, the choice of drug being empiric or based on invasive electrophysiologic investigation.

No current strategy for ventricular arrhythmia prophylaxis or treatment in acute MI is satisfactory. More complete knowledge of arrhythmia mechanisms, improved drugs and well-controlled studies are necessary if this aspect of clinical management is to be scientifically based.

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